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23 OCT 1991

Your reference
T1092GC

Notes

Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071–438 4700).

Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.

The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

❶ Title of invention

1 Please give the title of the invention: Therapeutic Agents

❷ Applicant's details

❷ Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

❑ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name: Merck Sharp & Dohme Limited

Country *(and State of incorporation, if appropriate)*: United Kingdom

Warning

After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977 and will inform the applicant if such prohibition or restriction is necessary. Applicants resident in the United Kingdom are also reminded that under Section 23, applications may not be filed abroad without written permission unless an application has been filed not less than 6 weeks previously in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction revoked.

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases**, please give the following details:

Address: Hertford Road
Hoddesdon
Hertfordshire

UK postcode *(if applicable)*: EN11 9BU

Country: United Kingdom

ADP number *(if known)*: 0597799001

2d, 2e and 2f: If there are further applicants please provide details on a separate sheet of paper.

❑ **Second applicant** ***(if any)***

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2f **In all cases**, please give the following details:

Address

UK postcode *(if applicable)*

Country

ADP number *(if known)*

❸ An address for service in the United Kingdom must be supplied

Please mark correct box

❸ Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ***go to 3b***

please give details below

Agent's name Dr. J. Thompson

Agent's address Merck & Co., Inc.
European Patent Department
Terlings Park
Eastwick Road
Harlow, Essex

Postcode CM20 2QR

Agent's ADP number ~~4392742002~~
4396653001

3b: If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

Address

Postcode

Daytime telephone number *(if available)*

ADP number *(if known)*

❹ Reference number

4 Agent's or applicant's reference number *(if applicable)* T1092GC

❺ Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ ***go to 6***

⬇ ***please give details below***

❏ number of earlier application or patent number

❏ filing date

(day month year)

❏ and the Section of the Patents Act 1977 under which you are claiming:

Please mark correct box

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

❻ Declaration of priority

❻ *If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.*

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day, month, year)*

❼ The answer must be 'No' if:
- any applicant is not an inventor
- there is an inventor who is not an applicant, **or**
- any applicant is a corporate body.

❼ Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark correct box

Yes [ ] No [X] ➡ ***A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).***

❽ Please supply duplicates of claim(s), abstract, description and drawing(s).

❽ Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77	–
Claim(s)	–
Description	75
Abstract	–
Drawing(s)	–

Please mark correct box(es)

8b Which of the following documents also accompanies the application?

Priority documents *(please state how many)*	–
Translation(s) of Priority documents *(please state how many)*	–
Patents Form 7/77 – Statement of Inventorship and Right to Grant *(please state how many)*	–
Patents Form 9/77 – Preliminary Examination/Search	–
Patents Form 10/77 – Request for Substantive Examination	–

❾ You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

❾ Request

I/We request the grant of a patent on the basis of this application.

Please sign here ➡

Signed J. Thompson
Dr. J. Thompson
Chartered Patent Agent

Date 23.10.91
(day month year)

A completed fee sheet should preferably accompany the fee.

Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to either:

❑ ***The Comptroller***
The Patent Office
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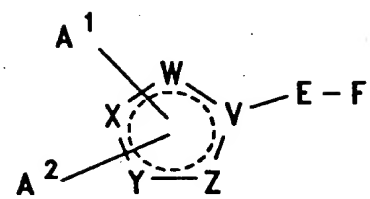


(I)

wherein the broken circle represents two non-adjacent double bonds in any position in the five-membered ring;

two, three or four of V, W, X, Y and Z represent nitrogen and the remainder represent carbon provided that, when two of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, then the said nitrogen atoms are in non-adjacent positions within the five-membered ring;

A^1 represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $-OR^x$, $-SR^x$, $-NR^xR^y$, $-NR^xCOR^y$, $-NR^xCO_2R^y$, $-NR^xSO_2R^y$, or $-NR^zCTNR^xR^y$;

A^2 represents a non-bonded electron pair when four of V, W, X, Y and Z represent nitrogen and the other represents carbon; or, when two or three of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, A^2 represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $-OR^x$, $-SR^x$, $-NR^xR^y$, $-NR^xCOR^y$, $-NR^xCO_2R^y$, $-NR^xSO_2R^y$, or $-NR^zCTNR^xR^y$;

E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

F represents a group of formula

THERAPEUTIC AGENTS

The present invention relates to a class of indole-substituted imidazole, triazole and tetrazole derivatives which act on 5-hydroxytryptamine (5-HT) receptors, being selective agonists of so-called "5-HT_1-like" receptors. They are therefore useful in the treatment of clinical conditions for which a selective agonist of these receptors is indicated.

5-HT_1-like receptor agonists which exhibit selective vasoconstrictor activity have recently been described as being of use in the treatment of migraine (see, for example, A. Doenicke et al., The Lancet, 1988, Vol. 1, 1309-11). The compounds of the present invention, being selective 5-HT_1-like receptor agonists, are accordingly of particular use in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania and headache associated with vascular disorders.

EP-A-0313397 describes a class of tryptamine derivatives substituted by a five-membered heteroaliphatic ring, which are stated to be specific to a particular type of "5-HT_1-like" receptor and thus to be effective therapeutic agents for the treatment of clinical conditions, particularly migraine, requiring this activity. However, EP-A-0313397 neither discloses nor suggests the imidazole, triazole and tetrazole derivatives provided by the present invention.

The present invention provides a compound of formula I, or a salt or prodrug thereof:

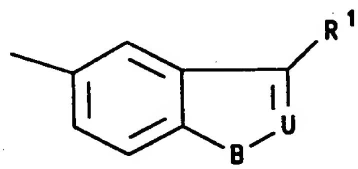
The present invention also provides compounds of formula I above wherein three or four of V, W, X, Y and Z represent nitrogen and the remainder represent carbon;

A^2 represents a non-bonded electron pair when four of V, W, X, Y and Z represent nitrogen and the other represents carbon; or, when three of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, A^2 represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $-OR^x$, $-SR^x$, $-NR^xR^y$, $-NR^xCOR^y$, $-NR^xCO_2R^y$, $-NR^xSO_2R^y$, or $-NR^zCTNR^xR^y$; and

A^1, E, F, R^x, R^y, R^z and T are as defined above.

For use in medicine, the salts of the compounds of formula I will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing

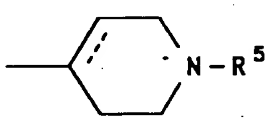
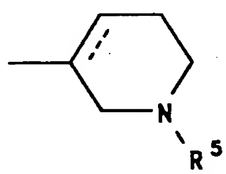
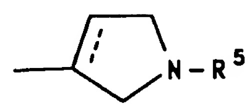


;

U represents nitrogen or $C-R^2$;

B represents oxygen, sulphur or $N-R^3$;

R^1 represents $-CH_2.CHR^4.NR^6R^7$ or a group of formula

 ,  or 

in which the broken line represents an optional chemical bond;

R^2, R^3, R^4, R^5, R^6 and R^7 independently represent hydrogen or C_{1-6} alkyl;

R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^x and R^y together represent a C_{2-6} alkylene group;

R^z represents hydrogen, hydrocarbon or a heterocyclic group;

T represents oxygen, sulphur or a group of formula =N.G; and

G represents hydrocarbon, a heterocyclic group or an electron-withdrawing group.

Particular aryl(C_{1-6})alkyl groups include benzyl, phenethyl and phenylpropyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidyl, piperidyl, piperazinyl and morpholinyl groups.

Suitable heteroaryl groups include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, imidazolyl, oxadiazolyl and thiadiazolyl groups.

Particular heteroaryl(C_{1-6})alkyl groups include pyridylmethyl and pyrazinylmethyl.

The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups selected from C_{1-6} alkyl, adamantyl, phenyl, halogen, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, aryloxy, keto, C_{1-3} alkylenedioxy, nitro, cyano, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkoxycarbonyl(C_{1-6})alkyl, C_{2-6} alkylcarbonyloxy, arylcarbonyloxy, C_{2-6} alkylcarbonyl, arylcarbonyl, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, arylsulphonyl, NR^vR^w, $-NR^vCOR^w$, $-NR^vCO_2R^w$, $-NR^vSO_2R^w$, $-CH_2NR^vSO_2R^w$, $-NHCONR^vR^w$, $-CONR^vR^w$, $-SO_2NR^vR^w$ and $-CH_2SO_2NR^vR^w$, in which R^v and R^w independently represent hydrogen, C_{1-6} alkyl, aryl or aryl(C_{1-6})alkyl, or R^v and R^w together represent a C_{2-6} alkylene group.

When R^x and R^y, or R^v and R^w, together represent a C_{2-6} alkylene group, this group may be an ethylene, propylene, butylene, pentamethylene or hexamethylene group, preferably butylene or pentamethylene.

When the group G represents an electron-withdrawing group, this group is suitably cyano, nitro, $-COR^x$, $-CO_2R^x$ or $-SO_2R^x$, in which R^x is as defined above.

up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl and aryl(C_{1-6})alkyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl and heteroaryl(C_{1-6})alkyl groups.

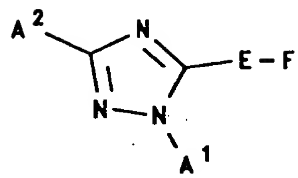
Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl and t-butyl.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl groups.

Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

A particular aryl group is phenyl.



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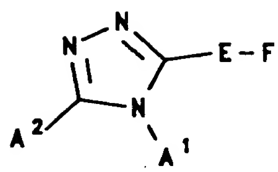

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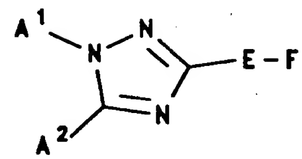

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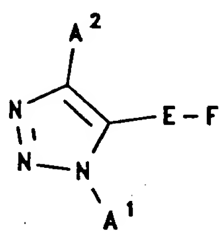

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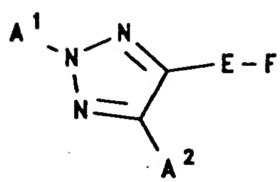

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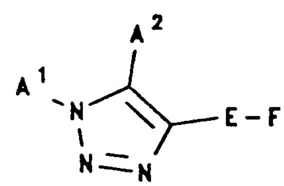

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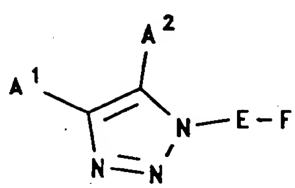

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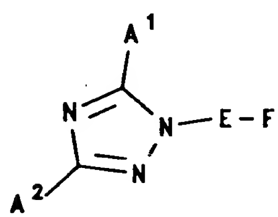

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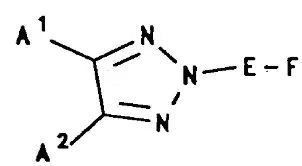


(IJ)

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine.

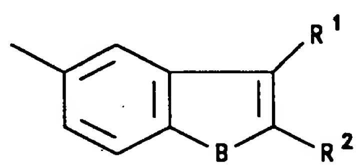
The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

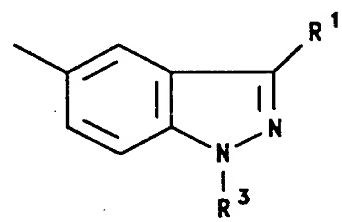
It will be appreciated that the imidazole, triazole and tetrazole rings of formula I can exist in a variety of canonical forms. These may suitably be represented by formulae IA to IT as follows:

2-methylpropylene. Alternatively, the group E may represent a single bond such that the group F in formula I is attached directly to the five-membered heteroaromatic ring.

The group F is suitably an indole, benzofuran or benzthiophene moiety of formula FA, or an indazole moiety of formula FB:

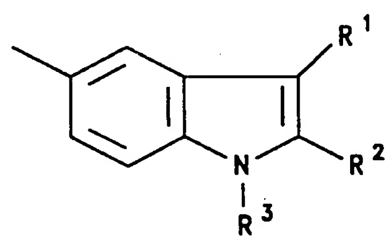


(FA)



(FB)

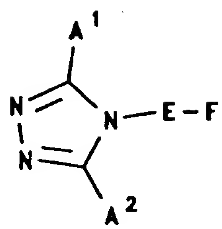
wherein B, R^1, R^2 and R^3 are as defined above. Preferably, the group F represents an indole moiety of structure FC:



(FC)

wherein R^1, R^2 and R^3 are as defined above, in particular wherein R^2 and R^3 are both hydrogen.

It will be appreciated that when four of V, W, X, Y and Z represent nitrogen and the other represents carbon, i.e. when the ring of formula I is a tetrazole ring, then the group A^2 will be a non-bonded electron pair. Otherwise, A^1 and A^2 will independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen,



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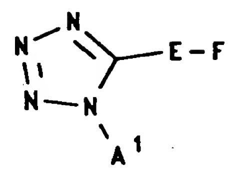

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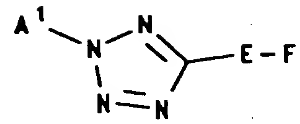

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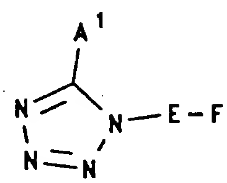

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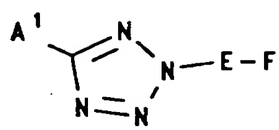

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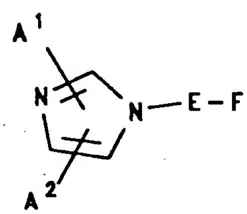

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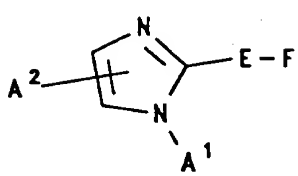

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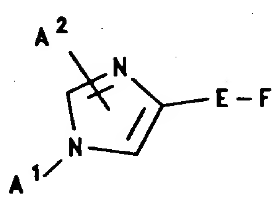

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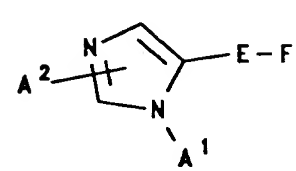


(IT)

wherein A^1, A^2, E and F are as defined above. Preferred imidazole, triazole and tetrazole rings of formula I include the rings represented by formulae IA, IC, IG, IH, IL, IM, IN, IP and IQ above, especially IH.

The alkylene chain E may be, for example, methylene, ethylene, 1-methylethylene, propylene or

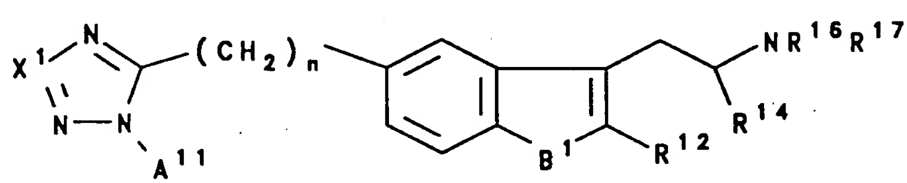
methylaminocarbonylphenyl, methylsulphonylaminomethylphenyl, aminosulphonylmethylphenyl, methylaminosulphonylmethylphenyl, dimethylaminosulphonylmethylphenyl, benzyl, trifluoromethylbenzyl, methoxybenzyl, acetylaminobenzyl, methylsulphonylaminobenzyl, aminocarbonylaminobenzyl, aminocarbonylbenzyl, methylaminocarbonylbenzyl, methylsulphonylbenzyl, methylaminosulphonylbenzyl, pyridylmethyl, methoxypyridylmethyl, amino, methylamino, benzylamino, dimethylamino, t-butoxycarbonylaminoethylamino and methylsulphonylaminoethylamino.

Preferred values of A^1 and/or A^2 include hydrogen, methyl, ethyl and benzyl.

Representative values of R^1 include aminoethyl, N-methylaminoethyl, N,N-dimethylaminoethyl and 1-methyl-4-piperidyl. Preferably, R^1 represents aminoethyl or N,N-dimethylaminoethyl.

Preferred values for the groups R^2 to R^7 are hydrogen and methyl.

A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA, and salts and prodrugs thereof:



(IIA)

wherein

X^1 represents nitrogen or A^{12}-C;

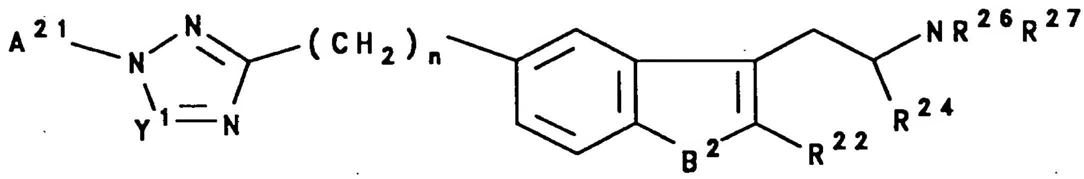
n is zero, 1, 2 or 3;

B^1 represents oxygen, suphur or N-R^{13};

cyano, trifluoromethyl, $-OR^x$, $-SR^x$, $-NR^xR^y$, $-NR^xCOR^y$, $-NR^xCO_2R^y$, $-NR^xSO_2R^y$, or $-NR^zCTNR^xR^y$.

Suitable values for the groups A^1 and/or A^2 include C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted; and hydrogen, halogen, cyano, trifluoromethyl, C_{1-6} alkoxy, C_{1-6} alkylthio or $-NR^xR^y$, in which R^x and R^y are as defined above. Examples of optional substituents on the groups A^1 and/or A^2 suitably include trifluoromethyl, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkylcarbonyl, C_{1-6} alkylsulphonyl, arylsulphonyl, amino, mono- or di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, arylcarbonylamino, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulphonylamino, arylsulphonylamino, C_{1-6} alkylsulphonylaminomethyl, aminocarbonylamino, mono- or di(C_{1-6})alkylaminocarbonylamino, mono- or diarylaminocarbonylamino, pyrrolidylcarbonylamino, aminocarbonyl, mono- or di(C_{1-6})alkylaminocarbonyl, C_{1-6} alkylaminosulphonyl, aminosulphonylmethyl, and mono- or di(C_{1-6})-alkylaminosulphonylmethyl.

Particular values of A^1 and/or A^2 include hydrogen, methyl, methoxymethyl, aminomethyl, dimethylaminomethyl, acetylaminomethyl, benzoylaminomethyl, t-butoxycarbonylaminomethyl, methylsulphonylaminomethyl, phenylsulphonylaminomethyl, aminocarbonylmethyl, ethyl, aminoethyl, acetylaminoethyl, benzoylaminoethyl, methoxycarbonylaminoethyl, ethoxycarbonylaminoethyl, t-butoxycarbonylaminoethyl, methylsulphonylaminoethyl, aminocarbonylaminoethyl, methylaminocarbonylaminoethyl, t-butylaminocarbonylaminoethyl, phenylaminocarbonylaminoethyl, pyrrolidylcarbonylaminoethyl, cyclopropyl, phenyl, methylsulphonylaminophenyl, aminocarbonylphenyl,



(IIB)

wherein

Y^1 represents nitrogen or A^{22}–C;

n is zero, 1, 2 or 3;

B^2 represents oxygen, sulphur or N–R^{23};

A^{21} and A^{22} independently represent C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl, C_{1-6} alkoxy, C_{1-6} alkylthio or $-NR^xR^y$;

R^{22}, R^{23}, R^{24}, R^{26} and R^{27} independently represent hydrogen or C_{1-6} alkyl; and

R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^x and R^y together represent a C_{2-6} alkylene group.

Examples of optional substituents on the groups A^{21} and A^{22} correspond to those indicated for the groups A^{11} and A^{12} with respect to formula IIA above. Particular values of A^{21} and A^{22} with respect to formula IIB include hydrogen, methyl, ethyl and benzyl.

Preferably, R^{22}, R^{23} and R^{24} each represents hydrogen. Preferred values of R^{26} and R^{27} with respect to formula IIB include hydrogen and methyl.

A^{11} and A^{12} independently represent C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl, C_{1-6} alkoxy, C_{1-6} alkylthio or $-NR^xR^y$;

R^{12}, R^{13}, R^{14}, R^{16} and R^{17} independently represent hydrogen or C_{1-6} alkyl; and

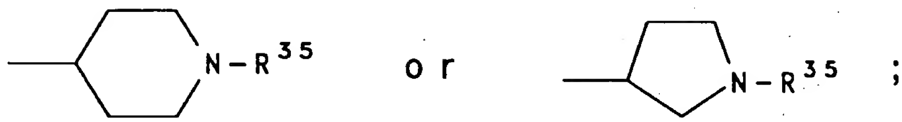
R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^x and R^y together represent a C_{2-6} alkylene group.

Examples of optional substituents on the groups A^{11} and A^{12} suitably include trifluoromethyl, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkylcarbonyl, C_{1-6} alkylsulphonyl, arylsulphonyl, amino, mono- or di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, arylcarbonylamino, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulphonylamino, arylsulphonylamino, C_{1-6} alkylsulphonylaminomethyl, aminocarbonylamino, mono- or di(C_{1-6})alkylamino-carbonylamino, mono- or diarylaminocarbonylamino, pyrrolidylcarbonylamino, aminocarbonyl, mono- or di(C_{1-6})alkylaminocarbonyl, C_{1-6} alkylaminosulphonyl, aminosulphonylmethyl, and mono- or di(C_{1-6})alkyl-aminosulphonylmethyl.

Particular values of A^{11} and A^{12} with respect to formula IIA include hydrogen, methyl, ethyl, benzyl and amino. When X^1 represents A^{12}-C, the group A^{11} is preferably hydrogen or methyl.

Preferably, R^{12}, R^{13} and R^{14} each represents hydrogen. Preferred values of R^{16} and R^{17} with respect to formula IIA include hydrogen and methyl.

Another sub-class of compounds according to the invention is represented by the compounds of formula IIB, and salts and prodrugs thereof:



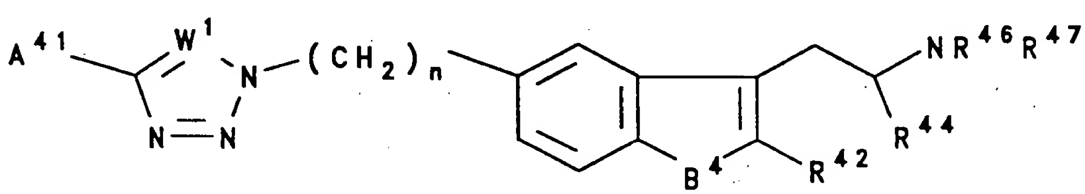
R^{32}, R^{33}, R^{34}, R^{35}, R^{36} and R^{37} independently represent hydrogen or C_{1-6} alkyl; and

R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^x and R^y together represent a C_{2-6} alkylene group.

Examples of optional substituents on the groups A^{31} and A^{32} correspond to those indicated for the groups A^{11} and A^{12} with respect to formula IIA above. Particular values of A^{31} and A^{32} with respect to formula IIC include hydrogen and methyl.

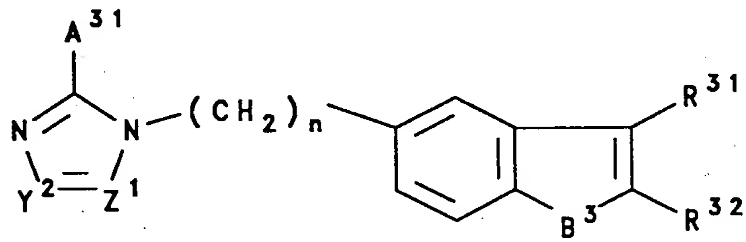
Preferably, R^{32}, R^{33} and R^{34} each represents hydrogen. Preferred values of R^{35}, R^{36} and R^{37} include hydrogen and methyl.

A still further sub-class of compounds according to the invention is represented by the compounds of formula IID, and salts and prodrugs thereof:



(IID)

A further sub-class of compounds according to the invention is represented by the compounds of formula IIC, and salts and prodrugs thereof:



(IIC)

wherein

Y^2 represents nitrogen or A^{32}-C;

Z^1 represents nitrogen or CH;

n is zero, 1, 2 or 3;

B^3 represents oxygen, sulphur or N-R^{33};

A^{31} and A^{32} independently represent C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl, C_{1-6} alkoxy, C_{1-6} alkylthio or $-NR^xR^y$;

R^{31} represents $-CH_2.CHR^{34}.NR^{36}R^{37}$ or a group of formula

N,N-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;
N,N-dimethyl-2-[5-(tetrazol-2-ylmethyl)-1H-indol-3-yl]ethylamine;
N,N-dimethyl-2-[5-(tetrazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;
N,N-dimethyl-2-[5-(1-methyl-1,2,4-triazol-5-ylmethyl)-1H-indol-3-yl]ethylamine;
N,N-dimethyl-2-[5-(1-methyl-1,2,4-triazol-3-ylmethyl)-1H-indol-3-yl]ethylamine;
N,N-dimethyl-2-[5-(1,2,3-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;
3-(2-aminoethyl)-5-(1-methyltetrazol-5-yl)-benzo[b]thiophene;
3-(2-aminoethyl)-5-(2-methyltetrazol-5-yl)-benzo[b]thiophene;
3-[2-(N,N-dimethylamino)ethyl]-5-(2-methyltetrazol-5-yl)benzo[b]thiophene;
N,N-dimethyl-2-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;
N,N-dimethyl-2-[5-(imidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;
N,N-dimethyl-2-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]ethylamine;
N,N-dimethyl-2-[5-(2-ethyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine;
N,N-dimethyl-2-[5-(1-ethyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine;
N,N-dimethyl-2-[5-(1,2,4-triazol-1-yl)-1H-indol-3-yl]ethylamine;
1-methyl-4-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]piperidine;
1-methyl-4-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]piperidine;

wherein

W^1 represents nitrogen or $C-R^{42}$;

n is zero, 1, 2 or 3;

B^4 represents oxygen, sulphur or $N-R^{43}$;

A^{41} and A^{42} independently represent C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl, C_{1-6} alkoxy, C_{1-6} alkylthio or $-NR^xR^y$;

R^{42}, R^{43}, R^{44}, R^{46} and R^{47} independently represent hydrogen or C_{1-6} alkyl; and

R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^x and R^y together represent a C_{2-6} alkylene group.

Examples of optional substituents on the groups A^{41} and A^{42} correspond to those indicated for the groups A^{11} and A^{12} with respect to formula IIA above. Particular values of A^{41} and A^{42} with respect to formula IID include hydrogen and methyl.

Preferably, R^{42}, R^{43} and R^{44} each represents hydrogen. Preferred values of R^{46} and R^{47} include hydrogen and methyl.

Specific compounds within the scope of the present invention include:

2-[5-(2-benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine;

2-[5-(1-benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine;

N,N-dimethyl-2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine;

N,N-dimethyl-2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine;

or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

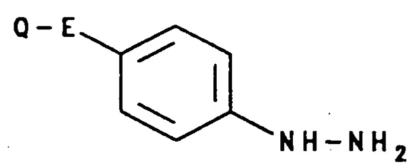
The 1,2,4-triazole compounds of this invention may be prepared by a process which comprises reacting a reactive derivative of a carboxylic acid of formula R^a-CO_2H with a compound either of formula III or of formula IV, or a salt thereof:

4-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]piperidine;
4-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]piperidine;
3-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]pyrrolidine;
and salts and prodrugs thereof.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, or suppositories, for oral, parenteral or rectal administration. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet

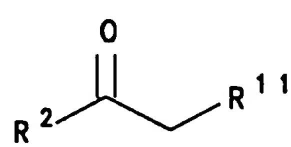
The reaction is conveniently carried out by heating the reagents together, optionally in a solvent, for example tetrahydrofuran, dimethylformamide or a lower alkanol such as ethanol, propanol or isopropanol, at about 20°C to 100°C for about 1 to 6 hours.

Where R^a is a group of formula -E-F and the group F is an indole moiety of structure FC as defined above, the reactive derivative of a carboxylic acid of formula HO_2C-E-F may be prepared by reacting a compound of formula VI:



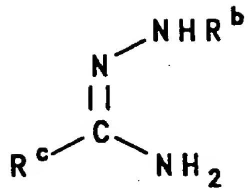
(VI)

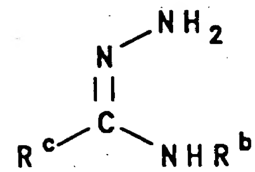
wherein Q represents a reactive carboxylate moiety, and E is as defined above; with a compound of formula VII or a carbonyl-protected form thereof:



(VII)

wherein R^2 is as defined above and R^{11} corresponds to the group R^1 as defined above or represents a group of formula $-CH_2.CHR^4D^1$, in which R^4 is as defined above and D^1 represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3.

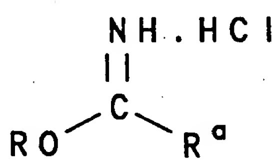

(III)


(IV)

wherein one of R^a, R^b and R^c is a group of formula A^1, another is a group of formula A^2, and the third is a group of formula -E-F, as defined with reference to formula I above.

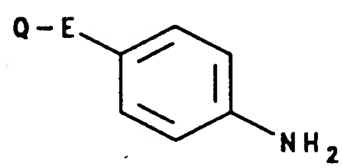
Suitable reactive derivatives of the acid R^a-CO_2H include esters, for example C_{1-4} alkyl esters; thioesters, for example pyridylthioesters; acid anhydrides, for example $(R^a-CO)_2O$; acid halides, for example acid chlorides; orthoesters; and primary, secondary and tertiary amides.

A preferred reactive derivative of the acid R^a-CO_2H is the iminoether derivative of formula V:


(V)

where R is C_{1-4} alkyl.

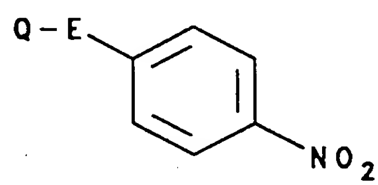
The reagent of formula III may be generated *in situ* in the reaction mixture. For example, the reaction may be effected by treating a compound of formula V above with an alkyl hydrazine, e.g. methyl hydrazine, followed by a suitable carboxylic acid such as formic acid.



(IX)

wherein Q and E are as defined above; by diazotisation followed by reduction. Diazotisation is typically carried out using sodium nitrite/conc. HCl and the resulting diazo product reduced <u>in situ</u> using, for example, tin(II) chloride/conc. HCl or sodium sulphite/conc. HCl.

The anilines of formula IX may be prepared by reduction of the corresponding nitro compounds of formula X:



(X)

wherein Q and E are as defined above; typically by catalytic hydrogenation or using tin(II) chloride.

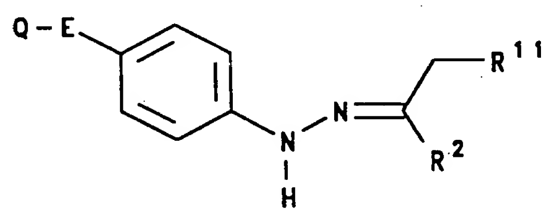
Where they are not commercially available, the nitro compounds of formula X may be synthesized by standard methods well known to those skilled in the art.

Where R^a is a group of formula -E-F and the group F is an indazole moiety of structure FB as defined above, the reactive derivative of a carboxylic acid of formula HO_2C-E-F may be prepared by the cyclisation of a compound of formula XI:

Suitable carbonyl-protected forms of the compounds of formula VII include the dimethyl acetal or ketal derivatives.

The readily displaceable group D^1 in the compounds of formula VII suitably represents a halogen atom, preferably chlorine. When the moiety R^{11} in the compounds of formula VII is a group of formula $-CH_2.CHR^4D^1$, the substituent D^1 is displaced <u>in situ</u> under the prevailing reaction conditions to afford a final product of formula I wherein R^1 represents a group of formula $-CH_2.CHR^4.NH_2$. The terminal amino group can subsequently, if desired, be further elaborated using techniques known from the art to give a compound of formula I wherein R^1 represents the required group of formula $-CH_2.CHR^4.NR^6R^7$.

The reaction of compounds VI and VII may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula VIII:



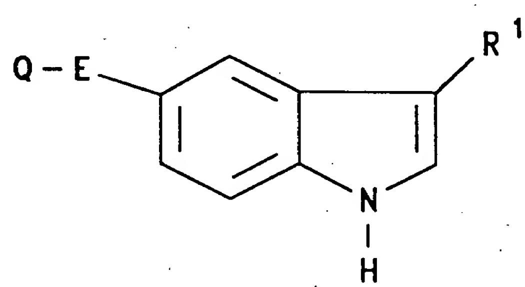
(VIII)

wherein Q, E, R^2 and R^{11} are as defined above; followed by cyclisation using a suitable reagent, such as a polyphosphate ester, to give a compound of formula Q-E-F.

The hydrazines of formula VI may be prepared from the corresponding anilines of formula IX:

the solvent; followed by acetylation with acetic anhydride, advantageously in the presence of a catalytic quantity of 4-dimethylaminopyridine, in dichloromethane at room temperature.

The N-formyl protected derivative of the intermediate of formula XII may be conveniently prepared by ozonolysis of an indole derivative of formula XIII:

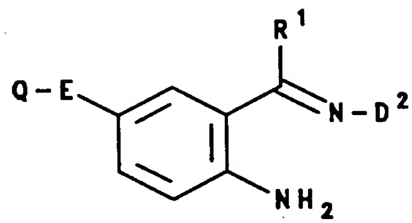


(XIII)

wherein R^1, E and Q are as defined above; followed by a reductive work-up, advantageously using dimethylsulphide.

The indole derivative of formula XIII may be prepared by methods analogous to those described in the accompanying Examples, or by procedures well known from the art.

In an alternative process, the triazole compounds according to the invention may be prepared by a method which comprises reacting a compound of formula XIV:

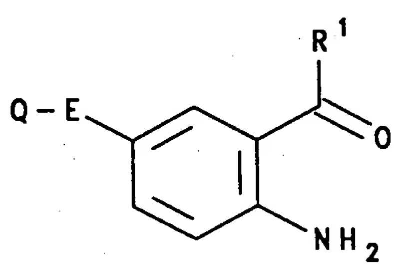


(XI)

wherein Q, E and R^1 are as defined above; and D^2 represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3.

The cyclisation of compound XI is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a mixture of m-xylene and 2,6-lutidine at a temperature in the region of 140°C.

The readily displaceable group D^2 in the compounds of formula XI suitably represents a C_{1-4} alkanoyloxy group, preferably acetoxy. Where D^2 in the desired compound of formula XI represents acetoxy, this compound may be conveniently prepared by treating a carbonyl compound of formula XII:



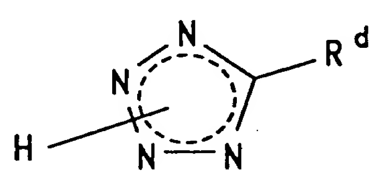
(XII)

wherein R^1, E and Q are as defined above; or a protected derivative thereof; with hydroxylamine hydrochloride, advantageously in pyridine at the reflux temperature of

azide of formula R^e-N_3, where one of R^d and R^e represents a group of formula A^1 and the other is a group of formula -E-F, as defined previously.

The cycloaddition reaction is conveniently effected by heating the reactants together at an elevated temperature, e.g. a temperature in the region of 150°C, in a suitable solvent such as N-methylpyrrolid-2-one, advantageously in the presence of triethylamine hydrochloride. The product obtained from the cycloaddition reaction will generally be a mixture of isomers substituted by the A^1 group at positions 1 and 2 of the tetrazole ring, corresponding to structures IL and IM respectively as defined above. These isomers may conveniently be separated using conventional techniques such as chromatography.

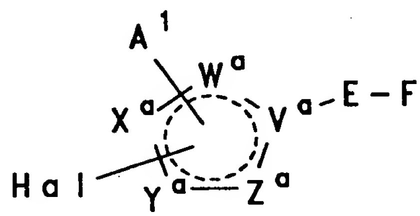
In an alternative process, the tetrazole compounds of the invention may be prepared by a method which comprises reacting a compound of formula R^e-L with a tetrazole derivative of formula XV:



(XV)

wherein one of R^d and R^e represents a group of formula A^1 and the other is a group of formula -E-F, as defined above, and L represents a suitable leaving group; in the presence of a base such as triethylamine.

The leaving group L suitably represents halogen, e.g. bromine or iodine, or a sulphonate derivative such as tosylate or mesylate.



(XIV)

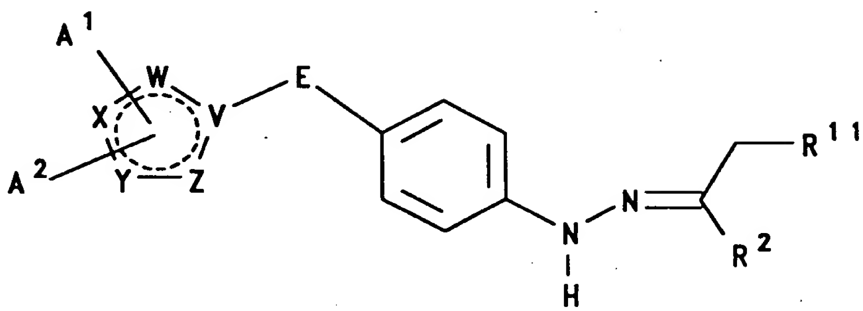
wherein A^1, E and F are as defined above, Hal represents halogen, and two of V^a, W^a, X^a, Y^a and Z^a, to one of which the group Hal is attached, represent carbon and the remainder represent nitrogen; with a reagent which provides an anion $^{-}A^2$, where A^2 is as previously defined.

Reagents which may provide the anion $^{-}A^2$ include Grignard reagents A^2MgHal (where Hal = halogen); organocuprate reagents such as $LiA^2{}_2Cu$; organolithium reagents A^2Li; or compounds which stabilise the anion by means of an adjacent activating group such as an ester or enolisable ketone function. In this case, the adjacent ester or ketone function may be retained after the process is complete, or may be removed. For example, an ester moiety may be hydrolysed and decarboxylated.

The 1,2,3-triazole compounds according to the present invention may be prepared by a process which comprises the cycloaddition of an alkyne of formula $R^a-C\equiv C-R^b$ with an azide of formula R^c-N_3, where R^a, R^b and R^c are as defined above.

The cycloaddition reaction may be conveniently effected in a suitable solvent such as tetrahydrofuran, ideally by heating in an autoclave for 8 hours.

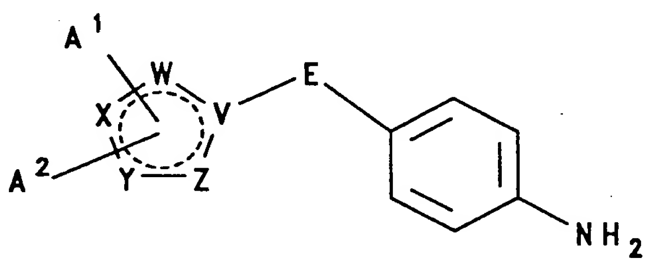
The tetrazole compounds in accordance with the invention may be prepared by a process which comprises the cycloaddition of a nitrile of formula $N\equiv C-R^d$ with an



(XVII)

wherein V, W, X, Y, Z, A^1, A^2, E, R^2 and R^{11} are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

The hydrazines of formula XVI may be prepared from the corresponding anilines of formula XVIII:



(XVIII)

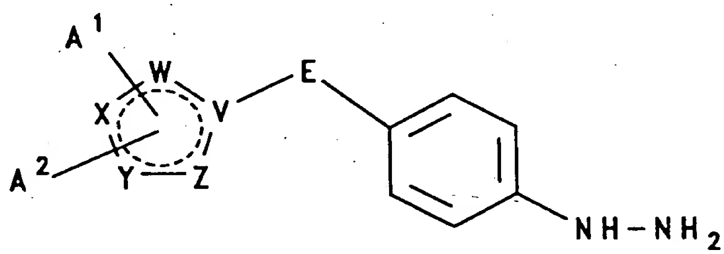
wherein V, W, X, Y, Z, A^1, A^2 and E are as defined above; by methods analogous to those described above with reference to the compounds of formula IX.

The anilines of formula XVIII may be prepared from the corresponding nitro compounds of formula XIX:

The reaction is conveniently carried out in a suitable organic solvent, e.g. acetonitrile, at room temperature.

The tetrazole derivatives of formula XV may be prepared by cycloaddition of a nitrile of formula $N{\equiv}C{-}R^d$ with sodium azide, advantageously under the conditions described above for the reaction between the nitrile $N{\equiv}C{-}R^d$ and the azide $R^e{-}N_3$; followed by acidification with a mineral acid such as hydrochloric acid.

In a further process, the compounds according to the invention wherein the group F is an indole moiety of structure FC as defined above may be prepared by a method which comprises reacting a compound of formula XVI:



(XVI)

wherein V, W, X, Y, Z, A^1, A^2 and E are as defined above; with a compound of formula VII as defined above, or a carbonyl-protected form thereof, e.g. the dimethyl acetal or ketal; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3.

As with that between compounds VI and VII, the reaction between compounds XVI and VII may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula XVII:

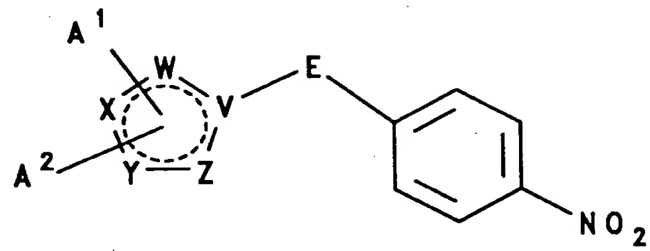
salts of the compounds of formula XX are commercially available, e.g. the sodium salt of 1,2,4-triazole, these are advantageously utilised in N,N-dimethylformamide solution in place of the compounds of formula XX themselves, with no requirement in this instance for additional base to be present in the reaction mixture.

The readily displaceable group D^3 in the compounds of formula XXI is suitably a halogen atom, preferably bromine; except when the moiety D^3 is attached directly to the aromatic ring, i.e. when E represents a bond, in which case D^3 is preferably fluorine.

Where they are not commercially available, the nitro compounds of formula XXI above may be prepared by procedures analogous to those described in the accompanying Examples, or by methods well known from the art.

In an alternative approach to the 1,2,4-triazole derivatives, the nitro compounds of formula XIX may be prepared from those of formula X above by appropriate modification of the moiety Q using, for example, methods analogous to those described above with reference to the compounds of formulae III and IV. Thus, for example, since Q in the compounds of formula X represents a reactive carboxylate moiety, the compounds of formula XIX may be prepared therefrom by reaction with a compound of formula $A^2\text{-}C(=NNHA^1)NH_2$ or $A^2\text{-}C(=NNH_2)NHA^1$.

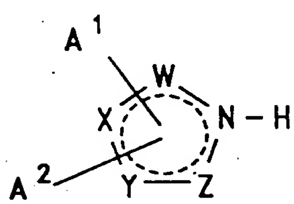
In a still further process, the compounds according to the invention wherein the group F is an imidazole moiety of structure FB as defined above may be prepared by a method which comprises cyclising a compound of formula XXII:



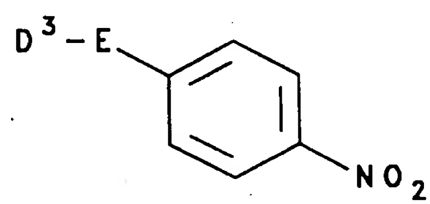
(XIX)

wherein V, W, X, Y, Z, A^1, A^2 and E are as defined above; by methods analogous to those described above with reference to the compounds of formula X.

The nitro compounds of formula XIX may be prepared by a variety of methods which will be readily apparent to those skilled in the art. For example, where V represents a nitrogen atom, the relevant compounds of formula XIX may be prepared by reacting the anion of a compound of formula XX with a compound of formula XXI:



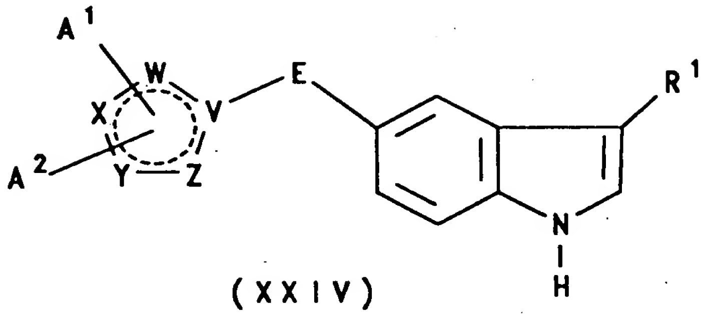
(XX)



(XXI)

wherein W, X, Y, Z, A^1, A^2 and E are as defined above, and D^3 represents a readily displaceable group.

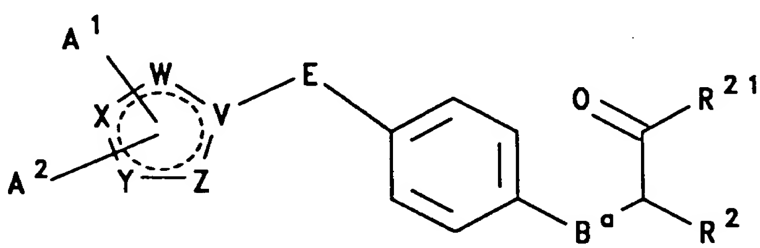
Where compound XX is a triazole or tetrazole derivative, the anion thereof may be generated by carrying out the reaction in a base such as triethylamine. Where compound XX is an imidazole derivative, the anion thereof may conveniently be generated if the reaction is carried out in sodium hydride using N,N-dimethylformamide as solvent. Where



(XXIV)

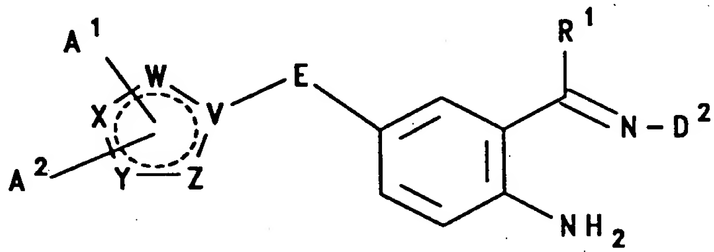
wherein V, W, X, Y, Z, A^1, A^2, E and R^1 are as defined above; using methods analogous to those described above with reference to the compounds of formulae XII and XIII. Thus, for example, since Q in the compounds of formula XIII represents a reactive carboxylate moiety, the 1,2,4-triazole derivatives of formula XXIV may be prepared therefrom by reaction with a compound of formula A^2-C(=NNHA^1)NH^2 or A^2-C(=NNH_2)NHA^1.

In a yet further process, the compounds according to the invention wherein the group F is a benzofuran or benzthiophene moiety may be prepared by a method which comprises cyclising a compound of formula XXV:



(XXV)

wherein V, W, X, Y, Z, A^1, A, E and R^2 are as defined above; B^a represents oxygen or sulphur; and R^{21} corresponds to the group R^1 as defined above, or represents a precursor group thereto as discussed below.

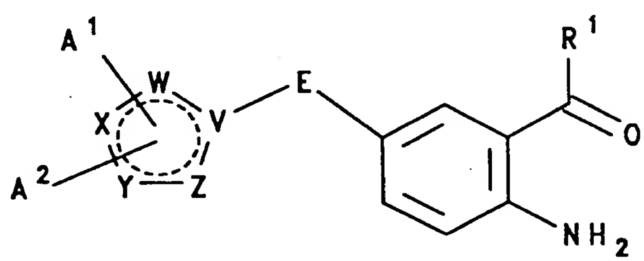


(XXII)

wherein V, W, X, Y, Z, A^1, A^2, E, R^1 and D^2 are as defined above; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3.

As with the cyclisation of compound XI, that of compound XXII is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a mixture of m-xylene and 2,6-lutidine at a temperature in the region of 140°C.

The compounds of formula XXII may, for example, be prepared from the corresponding compound of formula XXIII:



(XXIII)

wherein V, W, X, Y, Z, A^1, A^2, E and R^1 are as defined above; or a protected derivative thereof; which in turn may be prepared from the corresponding compound of formula XXIV:

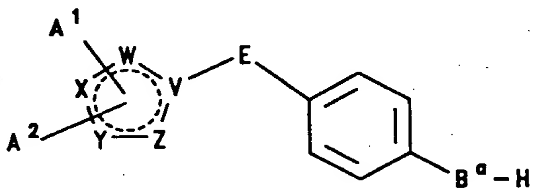
The compounds of formula XXVII and XXVIII, where they are not commercially available, may be prepared by standard procedures well known in the art.

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. Indeed, as will be appreciated, the compound of formula XV above in which R^d is a group of formula -E-F is itself a compound of formula I in which A^1 is hydrogen and A^2 represents a non-bonded electron pair. In particular, a compound of formula I wherein R^3 is hydrogen initially obtained may be converted into a compound of formula I wherein R^3 represents C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl by standard techniques such as alkylation, for example by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g. sodium hydride in dimethylformamide, or triethylamine in acetonitrile. Similarly, a compound of formula I wherein R^1 represents a group of formula $-CH_2.CHR^4.NH_2$ initially obtained may be converted into a compound of formula I wherein R^1 represents a group of formula $-CH_2.CHR^4.NR^6R^7$ in which R^6 and R^7 are as defined above with the exception of hydrogen, for example by conventional N-alkylation or N-arylation techniques, e.g. by treatment with the appropriate aldehyde in the presence of a reducing agent such as sodium cyanoborohydride.

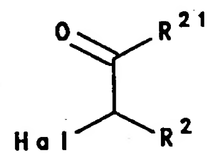
Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography.

The cyclisation is conveniently effected by using polyphosphoric acid or a polyphosphate ester, advantageously at an elevated temperature.

The compounds of formula XXV may be prepared by reacting a compound of formula XXVI with a compound of formula XXVII:



(XXVI)

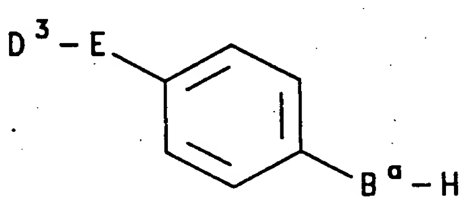


(XXVII)

wherein V, W, X, Y, Z, A^1, A^2, E, B^a, R^2 and R^{21} are as defined above, and Hal repesents halogen.

The reaction is conveniently effected in the presence of a base such as sodium hydroxide.

The hydroxy and mercapto derivatives of formula XXVI may be prepared by a variety of methods which will be readily apparent to those skilled in the art. In one such method, the anion of a compound of formula XX as defined above is reacted with a compound of formula XXVIII:



(XXVIII)

wherein D^3, E and B^a are as defined above; to afford an intermediate of formula XXVI wherein V is nitrogen.

by treatment with N-bromosuccinimide and benzoyl peroxide, in the presence of a bright light source, followed by reaction of the resulting bromo intermediate with sodium cyanide in dimethyl sulphoxide.

The following Examples illustrate the preparation of compounds according to the invention.

The ability of test compounds to bind to $5\text{-}HT_1$-like receptors was measured in membranes prepared from pig caudate using the procedure described in J. Neurosci., 1987, 7, 894. Binding was determined using 2 nM 5-hydroxytryptamine creatinine sulphate, 5-[1,2-^{3}H(N)] as a radioligand. Cyanopindolol (100 nM) and mesulergine (100 nM) were included in the assay to block out $5\text{-}HT_{1A}$ and $5\text{-}HT_{1C}$ binding sites respectively. The concentration of the compounds of the accompanying Examples required to displace 50% of the specific binding (IC_{50}) is below 1 μM in each case.

The activity of test compounds as agonists of the $5\text{-}HT_1$-like receptor was measured in terms of their ability to mediate contraction of the saphenous vein of New Zealand White rabbits, using the procedure described in Arch. Pharm., 1990, 342, 111. Agonist potencies were calculated as $-\log_{10}EC_{50}$ (pEC_{50}) values, from plots of percentage 5-HT (1 μm) response against the concentration of the agonist. The compounds of the accompanying Examples were found to possess pEC_{50} values in this assay of not less than 5.0 in each case.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1981. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

Alternatively, certain of the functional groups on the desired products may be carried through the reaction sequence as precursor groups, and then regenerated from these precursor groups at a late stage in the overall synthesis. For example, where R^1 in the desired compound of formula I represents a group of formula $-(CH_2)_2NH_2$, this group can be generated from a cyano precursor $-CH_2CN$ by reduction using, for example, borane/tetrahydrofuran. The cyano precursor may in turn be carried through the reaction sequence as a methyl group $-CH_3$, which may conveniently be converted to $-CH_2CN$

2. 2-(5-Cyanomethyl-1H-indol-3-yl)ethylamine. Hydrochloride

4-Chlorobutanal dimethylacetal (37.07g, 0.24mol) was added to a stirred solution of 4-hydrazinobenzyl cyanide hydrochloride (47.0g, 0.26mol) in $EtOH/H_2O$ (5:1; 21) and refluxed for 4.5h. The reaction mixture was evaporated to dryness under vacuum, MeOH (150ml) added, and the mixture left at 0°C for 10h. The resultant pale yellow precipitate was filtered under vacuum, washed with Et_2O/MeOH (5:1; 2 x 100ml) and dried. The product was used without further purification (24.1g, 40%), m.p. 239-241°C; R_f 0.4 in $CH_2Cl_2/EtOH/NH_3$ (40:8:1); ^1H NMR (360MHz, D_2O) 3.18 (2H, t, J = 7.1Hz, CH_2); 3.36 (2H, t, J = 7.1Hz, CH_2); 4.02 (2H, s, CH_2); 7.22 (1H, dd, J = 1.5 and 8.4Hz, Ar-H); 7.36 (1H, s, Ar-H); 7.56 (1H, d, J = 8.4Hz, Ar-H); 7.66 (1H, s, Ar-H).

3. 2-(5-Tetrazol-5-ylmethyl-1H-indol-3-yl) ethylamine

A solution of 2-(5-cyanomethyl-1H-indol-3-yl)ethylamine hydrochloride (2.5g, 10.6mmol), triethylamine hydrochloride (2.2g, 16.0mmol) and sodium azide (2.1g, 32.3mmol), in 1-methylpyrrolidin-2-one (30ml) was heated at 140°C for 8h. 5N hydrochloric acid (3ml) was added and the solvents removed by distillation under vacuum. The residue was chromatographed on silica-gel eluting with $EtOH/Et_2O/H_2O/NH_3$ (20:30:8:1) to give the title-tetrazole (1.76g, 69%); δ (360MHz, CD_3OD) 3.06 (2H, t, J = 7.2Hz, CH_2); 3.19 (2H, t, J = 7.2Hz, CH_2); 4.29 (2H, s,

EXAMPLE 1

2-[5-(2-Benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

1. 4-Hydrazinobenzylcyanide. Hydrochloride

A solution of $NaNO_2$ (80g, 1.16mol) was added dropwise to a cooled (-10°C), stirred, suspension of 4-aminobenzyl cyanide (153.5g, 1.16mol) in concentrated HCl (1500ml), at such a rate that the temperature did not rise above -10°C. The mixture was stirred at -10°C for 0.25h before being filtered rapidly under vacuum into an addition funnel. The solution was added portionwise over a 0.25h period to a rapidly stirred mixture of $SnCl_2.2H_2O$ (1.05kg, 4.64mol) in concentrated HCl (800ml) keeping the temperature below -5°C. The mixture was allowed to warm to room temperature and stir for 0.25h before filtering the sandy coloured precipitate under vacuum and washing with ether (5 x 500ml). The resultant solid was dried over P_2O_5 in a vacuum oven (80°C) for 16h to give the title compound (213g, 100%), m.p. 181-183°C; ^1H NMR (360MHz, D_2O) δ 3.90 (2H, s, CH_2); 7.06 (2H, d, J = 8.7Hz, Ar-H); 7.40 (2H, d, J = 8.7Hz, Ar-H).

R.T. for 16h. The solvent was removed under vacuum and the residue chromatographed through silica-gel eluting with CH_2Cl_2/MeOH (97:3) to give 2-separated benzyl tetrazoles. The less polar isomer was identified as the 2-benzyl tetrazole (0.17g, 22.4%); δ (360MHz, $CDCl_3$) 1.43 (9H, s, 3 of CH_3); 2.90 (2H, t, J = 6.8Hz, CH_2); 3.41 (2H, br t, CH_2); 4.32 (2H, s, CH_2); 5.70 (2H, s, $C\underline{H}_2$Ph); 7.00 (1H, s, Ar-H); 7.15 (1H, d, J = 8.4Hz, Ar-H); 7.28 (1H, d, J = 8.4Hz, Ar-H); 7.34 (5H, s, Ar-H); 7.50 (1H, s, Ar-H); 7.96 (1H, br s, NH).

The more polar component was identified as the 1-benzyltetrazole (0.2g, 26.4%) δ (360MHz, $CDCl_3$) 1.43 (9H, s, 3 of CH_3); 2.88 (2H, t, J = 7.0Hz, CH_2); 3.40 (1H, br t, CH_2); 4.26 (2H, s, CH_2); 5.29 (2H, s, $C\underline{H}_2$-Ph); 6.92 (1H, d, J = 8.4Hz, Ar-H); 7.01-7.05 (3H, m, Ar-H); 7.27-7.30 (5H, m, Ar-H); 8.08 (1H, br s, NH).

6. <u>2-[5-(2-Benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate</u>

Trifluoroacetic acid (1.5ml) was added to a solution of the less polar component isolated from step 5 (0.17g, 0.4mmol) in CH_2Cl_2 (5ml) and stirred at R.T. for 1h. The solvents were removed under vacuum and the residue chromatographed through silica-gel eluting with CH_2Cl_2/EtOH/NH_3 (40:8:1) to give the title-<u>tetrazole</u>. The oxalate salt was prepared (65mg); mp 169-171°C; (Found: C, 59.23; H, 5.07; N, 19.60.

CH_2); 7.07 (1H, d, J = 8.4Hz, Ar-H); 7.13 (1H, s, Ar-H); 7.29 (1H, d, J = 8.4Hz, Ar-H); 7.44 (1H, s, Ar-H).

4. N-tert-Butyloxycarbonyl-2-(5-tetrazol-5-ylmethyl-1H-indol-3-yl)ethylamine

To a stirred suspension of 2-(5-tetrazol-5-ylmethyl-1H-indol-3-yl)ethylamine (1.76g, 7.27mmol) in dry CH_2Cl_2 (40ml) was added triethylamine (1.5g, 14.9mmol) and $(BOC)_2O$ (1.9g, 7.3mmol) and the mixture stirred for 16h. The solvent was removed under vacuum and the residue chromatographed on silica-gel eluting with $EtOH/Et_2O/H_2O/NH_3$ (20:60:8:1) to give the title product (1.6g, 64%); δ (360MHz, CD_3OD) 1.41 (9H, s, 3 of CH_3); 2.87 (2H, t, J = 7.4Hz, CH_2); 3.30 (2H, t, J = 7.4Hz, CH_2); 4.32 (2H, s, CH_2); 6.99 (1H, d, J = 8.3Hz, Ar-H); 7.04 (1H, s, Ar-H); 7.26 (1H, d, J = 8.3Hz, Ar-H); 7.49 (1H, s, Ar-H).

5. N-tert-Butyloxycarbonyl-2-[5-(2-benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine and N-tert-butyloxycarbonyl-2-[5-(1-benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine

Benzyl bromide (0.31g, 1.8mmol) was added to a solution of the tetrazole from step 4 (0.62g, 1.8mmol), and triethylamine (0.37g, 3.6mmol) in dry acetonitrile (20ml). The mixture was stirred at R.T. for 2h, heated at 70°C for 1h and then stirred at

ylmethyl)-1H-indol-3-yl]ethylamine and N-tert-butyloxycarbonyl-2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine

Methyl iodide (0.44g, 3.1mmol) was added to a stirred solution of the tetrazole from step 4, Example 1 (0.95g, 2.78mmol) and triethylamine (0.56g, 5.5mmol) in dry acetonitrile (15ml). After 10h a further equivalent of methyl iodide was added and stirred for 16h. The solvent was removed under vacuum and the residue chromatographed on silica-gel eluting with CH_2Cl_2/MeOH (97:3) to give the title mixture of 1- and 2-methyltetrazoles (0.6g, 61%); δ (360MHz, $CDCl_3$) 1.43 (9H, m, 3 of CH_3); 2.89-2.92 (2H, m, CH_2); 3.38-3.48 (2H, m, CH_2); 3.83 (2H, s, CH_2); 4.28 and 4.40 (total 3H, s, CH_3); 6.98 and 7.17 (total 1H, d, J = 8.4Hz, Ar-H); 7.02 and 7.06 (total 1H, s, Ar-H); 7.30 and 7.31 (total 1H, d, J = 8.4Hz, Ar-H); 7.43 and 7.54 (total 1H, s, Ar-H); 8.00 and 8.10 (total 1H, br s, NH).

2. 2-[5-(2-Methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine and 2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine

Prepared from the preceding methyltetrazoles using the procedure described in step 6, Example 1. The crude product was chromatographed on silica-gel eluting with CH_2Cl_2/EtOH/NH_3 (40:8:1) to give 2 separated components. The less polar product (0.1g, 24%) was identified as the 2-

$C_{19}H_{20}N_6 \cdot 1.05 (C_2H_2O_4)$ requires C, 59.36; H, 5.22; N, 19.68%); δ (360MHz, D_2O) 3.09 (2H, t, J = 6.9Hz, CH_2); 3.29 (2H, t, J = 6.9Hz, CH_2); 4.30 (2H, s, CH_2); 5.77 (2H, s, CH_2); 7.11 (1H, dd, J = 1.6 and 8.4Hz, Ar-H); 7.28 (1H, s, Ar-H); 7.32-7.34 and 7.39-7.41 (5H, m, Ar-H); 7.43 (1H, d, J = 8.4Hz, Ar-H); 7.51 (1H, s, Ar-H).

EXAMPLE 2

2-[5-(1-Benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Hydrochloride. Hemihydrate

Prepared from the more polar component isolated from step 5, Example 1, using the procedure described for step 6, Example 1. The hydrochloride hemihydrate salt was prepared; mp 210-213°C; (Found: C, 60.39; H, 5.88; N, 22.14. $C_{19}H_{20}N_6 \cdot HCl \cdot 0.5H_2O$ requires C, 60.39; H, 5.87; N, 22.24%); δ (250MHz, D_2O) 3.02 (2H, t, J = 6.8Hz, CH_2); 3.19 (2H, t, J = 6.8Hz, CH_2); 4.44 (2H, s, CH_2); 5.60 (2H, s, CH_2); 6.95-7.02 (3H, m, Ar-H); 7.16-7.25 (4H, m, Ar-H); 7.28 (1H, s, Ar-H); 7.40 (1H, d, J = 8.4Hz, Ar-H).

EXAMPLE 3

N,N-Dimethyl-2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

1. N-tert-Butyloxycarbonyl-2-[5-(2-methyltetrazol-5-

5.74; N, 22.53. $C_{15}H_{20}N_6.C_2H_2O_4$ requires C, 54.54; H, 5.92; N, 22.45%); δ (360MHz, D_2O) 2.91 (6H, s, 2 of CH_3); 3.21 (2H, t, J = 7.4Hz, CH_2); 3.47 (2H, t, J = 7.4Hz, CH_2); 4.30 (3H, s, CH_3); 4.34 (2H, s, CH_2); 7.17 (1H, dd, J = 1.5 and 8.4Hz, Ar-H); 7.33 (1H, s, Ar-H); 7.48 (1H, d, J = 8.4Hz, Ar-H); 7.59 (1H, s, Ar-H).

EXAMPLE 4

N,N-Dimethyl-2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

Prepared from 2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine (0.125g, 0.49mmol) using the procedure described in step 3, Example 3. The free base (0.11g, 80%) obtained was converted to the oxalate salt and recrystallised from MeOH/Et_2O; mp 176-177°C; (Found: C, 54.21; H, 5.84; N, 22.36. $C_{15}H_{20}N_6$. $C_2H_2O_4$ requires C, 54.54; H, 5.92; N, 22.45%); δ (360MHz, D_2O); 2.91 (6H, s, 2 of CH_3); 3.21 (2H, t, J = 7.4Hz, CH_2); 3.40 (2H, t, J = 7.4Hz, CH_2); 4.00 (3H, s, CH_3); 4.43 (2H, s, CH_2); 7.13 (1H, dd, J = 1.5 and 8.4Hz, Ar-H); 7.35 (1H, s, Ar-H); 7.50 (1H, d, J = 8.4Hz, Ar-H); 7.54 (1H, s, Ar-H).

EXAMPLE 5

N,N-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate Hemihydrate

methyltetrazole; δ (360MHz, $CDCl_3$) 1.38 (9H, s, 3 of CH_3); 2.88 (2H, t, J = 6.6Hz, CH_2); 3.00 (2H, t, J = 6.6Hz, CH_2); 4.28 (3H, s, CH_3); 4.33 (2H, s, CH_2); 7.00 (1H, d, J = 8.4Hz, Ar-H); 7.06 (1H, d, J = 2.1Hz, Ar-H); 7.17 (1H, d, J = 8.4Hz, Ar-H); 7.56 (1H, s, Ar-H); 8.04 (1H, br s, NH).

The more polar product (0.13g, 31%) was identified as the 1-methyltetrazole; δ (360MHz, $CDCl_3$) 1.38 (9H, s, 3 of CH_3); 2.86 (2H, t, J = 6.6Hz, CH_2); 3.00 (2H, t, J = 6.6Hz, CH_2); 3.82 (3H, s, CH_3); 4.40 (2H, s, CH_2); 6.98 (1H, dd, J = 1.6 and 8.3Hz, Ar-H); 7.06 (1H, d, J = 1.6Hz, Ar-H); 7.31 (1H, d, J = 8.3Hz, Ar-H); 7.41 (1H, s, Ar-H); 8.18 (1H, br s, NH).

3. N,N-Dimethyl-2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

A solution of formaldehyde (80mg of a 30% solution) in methanol (15ml) was added to a stirred solution of 2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine (0.1g, 0.4mmol), $NaCNBH_3$ (60mg) and glacial acetic acid (0.12g) in methanol (15ml). The solution was stirred for 2h, basified with K_2CO_3 solution and the MeOH removed under vacuum. The crude product obtained after extraction into ethylacetate and removal of solvent was chromatographed through silica-gel eluting with CH_2Cl_2/EtOH/NH_3 (40:8:1) to give the desired N,N-dimethyltryptamine (96mg, 87%). The oxalate salt was prepared: mp 185-187°C (MeOH/Et_2O); (Found: C, 54.42; H,

3. 1-(4-Hydrazinophenyl)methyl-1,2,4-triazole

A solution of sodium nitrite (3.28g, 48mmol) in water (20ml) was added to a solution of the preceding amine hydrochloride (10.0g, 48mmol), in concentrated HCl (40ml), at such a rate that the temperature did not exceed -10°C. After addition was complete the solution was stirred at 0°C for 0.25h and then added portionwise to a rapidly stirred solution of $SnCl_2.2H_2O$ (40g) in concentrated HCl (40ml). The solution was warmed to room temperature and basified with 20% aqueous NaOH solution. The solution was extracted with ethyl acetate (3 x 250ml) and the combined extracts dried ($MgSO_4$) and filtered through hyflo. The solution was evaporated to dryness to give the desired hydrazine (5.0g, 56%) m.p. 109-112°C. δ (360MHz, D_6-DMSO) 3.93 (2H, br s, NH_2), 5.20 (2H, s, CH_2), 6.73 (2H, d, J = 8Hz, Ar-H), 7.08 (2H, d, J = 8Hz, Ar-H), 7.92 (1H, s, Ar-H), 8.57 (1H, s, Ar-H).

4. 2-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl] ethylamine.

4-Chlorobutanal dimethylacetal (3.22g, 21.1mmol) was added to a stirred solution of the preceding hydrazine (5.0g, 26.4mmol) in ethanol/water (5:1, 180ml) and 5N HCl (4.5ml) and the solution refluxed for 4h. The solvents were removed under vacuum and the residue chromatographed on silica gel, eluting with CH_2Cl_2/EtOH/NH_3 (30:8:1) to give the desired tryptamine (2.4g, 38%). δ(360MHz, $CDCl_3$) 2.90 (2H, t, J = 7Hz,

1. 1-(4-Nitrophenyl)methyl-1,2,4-triazole

4-Nitrobenzylbromide (21.6g, 0.1mol) was added to a rapidly stirred suspension of 1,2,4-triazole sodium salt (9.1g, 0.1mol) in anhydrous DMF (100ml) and the mixture stirred at room temperature for 16h. Ethyl acetate (400ml) was added followed by water (250ml) and the layers separated. The organic phase was washed with water (3 x 250ml), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel eluting with ethyl acetate to give the title-product (10.6g, 52%); m.p. 98-100°C. δ (360MHz, $CDCl_3$) 5.47 (2H, s, CH_2) 7.40 (2H, d, J = 9Hz, Ar-H), 8.02 (1H, s, Ar-H), 8.18 (1H, s, Ar-H), 8.23 (2H, d, J = 9Hz, Ar-H).

2. 1-(4-Aminophenyl)methyl-1,2,4-triazole. Hydrochloride

A solution of 1-(4-nitrophenyl)methyl-1,2,4-triazole (10.0g, 49mmol) in ethanol (50ml), ethyl acetate (50ml), 5N HCl (10ml) and water (10ml) was hydrogenated over 10% Pd/C (1.0g) at 40 p.s.i., in a Parr apparatus, until an uptake of 188 p.s.i., had been observed (approx 10mins). The catalyst was removed by filtration through hyflo and the solvent removed under vacuum. The residue was azeotroped with ethanol (x2) to give the title-amine hydrochloride (10.6g, 100%). δ (360MHz, D_2O) 5.53 (2H, s, CH_2), 7.37-7.48 (4H, m, Ar-H), 8.12 (1H, s, Ar-H), 8.66 (1H, s, Ar-H).

EXAMPLE 6

N,N-Dimethyl-2-[5-(1,2,3,4-tetrazol-2-ylmethyl)-1H-indol-3-yl]ethylamine Oxalate.

1. 1-(4-Nitrophenyl)methyl-1,2,3,4-tetrazole and 2-(4-nitrophenyl)methyl-1,2,3,4-tetrazole.

4-Nitrobenzylbromide (15.42g, 71.3mmol) was added to a stirred solution of 1H-tetrazole (5.0g, 71.3mmol) and triethylamine (7.9g, 78.0mmol) in acetonitrile (100ml). The mixture was stirred at room temperature for 16h, the solvent removed under vacuum and the residue chromatographed on silica gel eluting with dichloromethane to give 2-isomers. The 2-alkylated product was obtained as the less polar product (2.47g, 17%); δ (360MHz, $CDCl_3$) 5.92 (2H, s, CH_2), 7.53 (2H, d, J = 8.7Hz, Ar-H), 8.25 (2H, d, J = 8.7Hz, Ar-H), 8.56 (1H, s, Ar-H). The more polar, major isomer was identified as the 1-alkylation product (11g, 75%); δ (360MHz, $CDCl_3$) 5.73 (2H, s, CH_2), 7.46 (2H, d, J = 8.7Hz, Ar-H), 8.27 (2H, d, J = 8.7Hz, Ar-H), 8.64 (1H, s, Ar-H).

2. 2-(4-Aminophenyl)methyl-1,2,3,4-tetrazole. Hydrochloride

2-(4-Nitrophenyl)methyl-1,2,3,4-tetrazole (2.47g, 12.1mmol) was hydrogenated as described for Example 5 step 2. The product (2.55g, 100%) was obtained as the hydrochloride

CH_2), 2.99 (2H, t, J = 7Hz, CH_2), 5.43 (2H, s, CH_2), 7.10 (1H, s, Ar-H), 7.11 (1H, d, J = 8Hz, Ar-H), 7.39 (1H, d, J = 8Hz, Ar-H), 7.57 (1H, s, Ar-H), 7.94 (1H, s, Ar-H), 8.08 (1H, s, Ar-H).

5. N,N-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine Oxalate Hemihydrate

A solution of formaldehyde (37% w/w solution, 0.19g), in methanol (10ml), was added to a mixture of the preceding tryptamine (0.36g, 1.5mmol), $NaCNBH_3$ (0.225g, 3.6mmol) and glacial acetic acid (0.45g), in methanol (10ml). The mixture was stirred at room temperature for 2h before adding saturated K_2CO_3 (50ml) and evaporating the methanol. The residue was extracted with ethyl acetate (3 x 100ml) and the combined extracts washed with brine (100ml), dried (K_2CO_3), and evaporated. The crude product was chromatographed on silica gel eluting with CH_2Cl_2/EtOH/NH_3 (20:8:1) to give the free base of the title-compound (0.21g, 52%). The oxalate hemihydrate salt was prepared, m.p. 165-167°C (MeOH/Et_2O); (Found: C, 55.53; H, 6.04; N, 18.59. $C_{15}H_{19}N_5.C_2H_2O_4.0.55H_2O$ requires C, 55.29; H, 6.03; N, 18.96%); m/e 269 (M^+); δ (360MHz, D_2O) 2.91 (6H, s, NMe_2), 3.22 (2H, t, J = 7Hz, CH_2), 3.47 (2H, t, J = 7Hz, CH_2), 5.52 (2H, s, CH_2), 7.21 (1H, dd, J = 1.6 and 8.4Hz, Ar-H), 7.36 (1H, s, Ar-H), 7.52 (1H, d, J = 8.4Hz, Ar-H), 7.65 (1H, s, Ar-H), 8.06 (1H, s, Ar-H), 8.56 (1H, s, Ar-H).

salt; δ (250MHz, D_2O) 5.86 (2H, s, CH_2), 7.40 (2H, d, J = 8.7Hz, Ar-H), 7.36 (2H, d, J = 8.7Hz, Ar-H), 8.74 (1H, s, Ar-H).

3. N,N-Dimethyl-2-[5-(1,2,3,4-tetrazol-2-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate.

The preceding amine was converted into the title-compound using the general procedures described for Example 5 Steps 3-5. The oxalate salt was prepared and recrystallised from MeOH/Et_2O; mp 198-199°C; (Found: C, 53.38; H, 5.55; N, 22.63. $C_{14}H_{18}N_6$. $C_2H_2O_4$. 0.2 (EtOH) requires C, 53.30; H, 5.78; N, 22.74%); δ(360MHz, D_2O) 2.91 (6H, s, NMe_2), 3.23 (2H, t, J = 7.4Hz, CH_2), 3.48 (2H, t, J = 7.4Hz, CH_2), 6.01 (2H, s, CH_2), 7.30 (1H, dd, J = 1.6 and 8.4Hz, Ar-H), 7.37 (1H, s, Ar-H), 7.53 (1H, d, J = 8.4Hz, Ar-H), 7.76 (1H, s, Ar-H), 8.74 (1H, s, Ar-H).

EXAMPLE 7

N,N-Dimethyl-2-[5-1,2,3,4-tetrazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Succinate

1-(4-nitrophenyl)methyl-1,2,3,4-tetrazole was converted into the title-compound using the procedures described for Example 5. The succinate salt was prepared, m.p. 55-56°C (isopropylalcohol); (Found C: 57.08; H, 6.14; N, 23.34. $C_{14}H_{18}N_6$. 0.75 ($C_4H_6O_4$) requires C, 56.89; H, 6.32; N,

23.42%); δ (360MHz,D_2O) 2.93 (6H, s, NMe_2), 3.23 (2H, t, J = 7.5Hz, CH_2), 3.48 (2H, t, J = 7.5Hz, CH_2), 5.81 (2H, s, CH_2), 7.28 (1H, dd, J = 1.7 and 8.4Hz, Ar-H), 7.39 (1H, s, Ar-H), 7.56 (1H, d, J = 8.4Hz, Ar-H), 7.75 (1H, s, Ar-H), 9.20 (1H, s, Ar-H).

EXAMPLE 8

N,N-Dimethyl-2-[5-(1-methyl-1,2,4-triazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Bisoxalate

1. Ethyl 3-[2-(dimethylamino)ethyl]-1H-indole-5-methylcarboximidate. Hydrochloride

A solution of N,N-dimethyl-2-(5-cyanomethyl-1H-indol-3-yl)ethylamine (5g, 22.01mmol) in ethanol was saturated with HCl gas and the solution stirred at room temperature for 16h. The solvent was removed under vacuum to give the title-product (6g, 92%); δ (360MHz, D_6-DMSO) 1.29 (3H, t, J = 7.0Hz, CH_2); 2.83 (6H, s, NMe_2), 3.13 (2H, t, J = 7.5Hz, CH_2), 3.31 (2H, m, CH_2), 4.04 (2H, s, CH_2), 4.42 (2H, q, J = 7.0Hz, CH_2), 7.08 (1H, dd, J = 1.5 and 8.4Hz, Ar-H), 7.27 (1H, s, Ar-H), 7.37 (1H, d, J = 8.4Hz, Ar-H), 7.48 (1H, br s, NH), 7.71 (1H, s, Ar-H).

2. N,N-Dimethyl-2-[5-(1-methyl-1,2,4-triazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Bisoxalate

was identified as the title-triazole (180mg). The trishydrochloride salt was prepared, mp <40°C (hygroscopic); Found: C, 49.80, H, 6.56; N, 16.69. $C_{16}H_{21}N_5$. 3HCl. 0.35 (Et_2O) requires C, 49.91; H, 6.62; N, 16.73%); δ (360MHz, D_2O) 2.91 (6H, s, NMe_2); 3.23 (2H, t, J = 7.4Hz, CH_2), 3.49 (2H, t, J - 7.4Hz, CH_2), 3.95 (3H, s, Me), 4.27 (2H, s, CH_2), 7.17 (1H, dd, J = 1.5 and 8.5Hz, Ar-H), 7.34 (1H, s, Ar-H), 7.50 (1H, d, J = 8.5Hz, Ar-H), 7.60 (1H, s, Ar-H), 8.88 (1H, s, Ar-H).

EXAMPLE 10

N,N-Dimethyl-2-[5-(1,2,3-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate.

1. 1-(4-nitrophenyl)methyl-1,2,3-triazole

4-Nitrobenzylbromide (25.4g, 0.12mol) was added to a solution of 1H-1,2,3-triazole (8.12g, 0.12mol) and triethylamine (11.88g, 0.12mol) in anhydrous acetonitrile. The mixture was refluxed for 1h, cooled to room temperature and the precipitated NEt_3. HBr filtered off. The solvent was removed under vacuum and the residue chromatographed through silica gel eluting with CH_2Cl_2 (100) to CH_2Cl_2/MeOH (95.5) to give 2-products. The more polar product was identified as the title-1-isomer (13g, 54%); mp 114-116°C δ (250MHz, $CDCl_3$) 5.72 (2H, s, CH_2), 7.38 (2H, d, J = 9Hz, Ar-H), 7.64 (1H, s, Ar-H), 7.78 (1H, s, Ar-H), 8.18 (2H, d, J = 9Hz, Ar-H). The less polar, minor isomer was

A mixture of the preceding imidate ester (3g, 10.15mmol), methylhydrazine (0.8ml) and triethylamine (3.54ml), in ethanol (30ml), was stirred at room temperature for 3h. The solvent was removed under vacuum and the resultant product dissolved in formic acid (98%, 3.3ml) and the solution stirred for 0.5h at room temperature and refluxed for 2h. The solution was cooled to room temperature, poured into an aqueous solution of K_2CO_3 (75ml) and extracted with ethyl acetate (4 x 200ml). The combined extracts were dried ($MgSO_4$) and evaporated, and the residue chromatographed through silica gel eluting with CH_2Cl_2/EtOH/NH_3 (40:8:1) to give 2-components. The less polar isomer was identified as the title-1-methyl-1,2,4-triazole (360mg). The bisoxalate salt was prepared; mp 135-137°C; (Found: C, 50.91; H, 5.38; N, 13.86. $C_{16}H_{21}N_5$. 0.25(ethanol) requires C, 50.70; H, 5.47; N, 14.08%); δ (360MHz, D_2O) 2.91 (6H, s, NMe_2); 3.23 (2H, t, J = 7.3Hz, CH_2), 3.48 (2H, t, J = 7.3Hz, CH_2), 3.95 (3H, s, Me), 4.48 (2H, s, CH_2), 7.13 (1H, dd, J = 1.5 and 8.4Hz, Ar-H), 7.37 (1H, s, Ar-H), 7.53 (1H, d, J = 8.4Hz, Ar-H), 7.57 (1H, s, Ar-H), 8.32 (1H, s, Ar-H).

EXAMPLE 9

N,N-Dimethyl-2-[5-(1-methyl-1,2,4-triazol-3-ylmethyl)-1H-indol-3-yl]ethylamine. Trishydrochloride

The more polar isomer obtained from Example 8 Step 2

To a stirred solution of 4-bromothiophenol (5.09g, 26.9mmol) in NaOH (1.08g, 26.9mmol) and water (32ml) was added chloroacetone (2.17ml, 27.3mmol) and the mixture was stirred under nitrogen for 45min before extracting with ether, washing with water, drying (Na_2SO_4) and evaporating *in vacuo*, leaving 6.89g (100%) of the title compound as a white solid, δ ($CDCl_3$) 2.27 (3H, s), 3.65 (2H, s), 7.20 (2H, d, J = 8.5Hz), 7.41 (2H, d, J = 8.5Hz).

Step 2

5-Bromo-3-methyl benzo[b)]thiophene

To a gently refluxing mixture of polyphosphoric acid (4.47g) and chlorobenzene (100ml) was added 4-bromophenylmercaptopropanone (2.24g, 9.14mmol) portionwise over 1h and the mixture was heated at reflux for 8 days. After cooling the organic phase was decanted off and the residue was decomposed with H_2O (~100ml), extracted with CH_2CI_2 (2 x 75ml), dried ($MgSO_4$) and combined with the decanted organic phase. This was evaporated *in vacuo* to leave 2.096g of brown oil. Distillation on a Kugelröhr apparatus yielded 1.83g (88%) of the title compound as a pale yellow liquid, bp 100-110°C/0.35mbar. δ ($CDCl_3$) 2.41 (3H, s), 7.10 (1H, s), 7.43 (1H, dd, J = 8.5 and 1.9Hz), 7.69 (1H, d, J = 8.5Hz), 7.64 (1H, d, J = 1.9Hz).

identified as the 2-alkylation product (2.25g, 9%), mp 112-113°C. δ (250MHz, $CDCl_3$) 5.72 (2H, s, CH_2), 7.40 (2H, d, J = 9Hz, Ar-H), 7.66 (2H, s, Ar-H), 8.18 (2H, d, J = 9Hz, Ar-H).

2. N,N-Dimethyl-2-[5-(1,2,3-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

1-(4-nitrophenyl)methyl-1,2,3-triazole was converted into the title-indole using the general procedures described for example 5. The oxalate salt was prepared mp 210-212°C, (Found: C, 55.88; H, 5.75; N, 18.69. $C_{15}H_{19}N_5$. 1.1($C_2H_2O_4$) 0.15H_2O requires C, 55.67; H, 5.84; N, 18.87%), δ (360MHz, D_2O). 2.90 (6H, s, NMe_2), 3.22 (2H, t, J = 7.4Hz, CH_2), 3.46 (2H, t, J - 7.4Hz, CH_2), 5.72 (2H, s, CH_2), 7.24 (1H, dd, J = 1.6 and 8.4Hz, Ar-H), 7.36 (1H, s, Ar-H), 7.52 (1H, d, J = 8.4Hz, Ar-H), 7.66 (1H, s, Ar-H), 7.79 (1H, s, Ar-H), 8.00 (1H, d, J = 1Hz, Ar-H)

EXAMPLE 11

3-(2-Aminoethyl)-5-(2-methyl-tetrazol-5-yl)benzo[b]thiophene. Oxalate.

Step 1

4-Bromophenylmercaptopropanone

leave 0.78g of a white solid. This was chromatographed on flash silica, eluting with CH_2CI_2/MeOH/NH_3(aq) (40:8:1 to 30:8:1), to give 0.246g (100%) of the title product as a white solid. δ (DMSO) 2.46 (3H, s), 7.41 (1H, s), 7.98 (1H, d, J = 8.4Hz), 8.03 (1H, dd, J = 8.4 and 1.5Hz), 8.36 (1H, d, J = 0.9Hz). *m/z* (CI^-, NH_3) 215 $(M-H)^-$, 160.

Step 5

3-Methyl-5-(2-methyltetrazol-5-yl)benzo[b]thiophene and 3-Methyl-5-(1-methyltetrazol-5-yl) benzo[b]thiophene

To a mixture of 3-Methyl-5-(tetrazol-5-yl) benzo[b]thiophene (0.241g, 1.12mmol) in acetonitrile (5ml) was added triethylamine (0.28ml, 2.01mmol), then iodomethane (0.486ml, 7.81mmol) followed by DMF (3ml) until a clear solution formed. The solution was stirred overnight under nitrogen before evaporating *in vacuo* and partitioning the residue between water (50ml) and ether (25ml). The aqueous layer was separated and extracted with more ether (2 x 25ml), the combined ether extracts were dried (Mg SO_4) and evaporated *in vacuo* to leave 0.241g of yellow solid. Chromatography on flash silica, eluting with 25-40% ethyl acetate/petroleum ether gave 0.168g (65%) of the 2-isomer of the title product as a white solid and 0.063g (24%) of the 1-isomer of the title product as a white solid. 2-isomer δ ($CDCl_3$) 2.52 (3H, s), 4.42 (3H, s), 7.14 (1H, s), 7.94 (1H, d, J = 8.4Hz), 8.10 (1H, dd,

Step 3

5-Cyano-3-methyl benzo[b]thiophene

To copper (I) cyanide (0.569g, 6.35mmol) was added 5-bromo-3-methyl benzo[b]thiophene (1.179g, 5.19mmol) in N-methylpyrrolidinone (10ml) and the mixture was stirred at 180-190°C for 17h. This was then partitioned between ether (75ml) and ammonia solution (75ml). The ether layer was separated, washed with more ammonia solution (2 x 50ml), dried (Na_2SO_4) and evaporated *in vacuo* to leave 0.81g of an off-white solid. Chromatography on flash silica, eluting with 10% ethyl acetate/petroleum ether yielded 0.76g (85%) of the title compound as a white solid. δ ($CDCl_3$) 2.47 (3H, s), 7.23 (1H, s), 7.55 (1H, dd, J = 8.3 and 1.5Hz), 7.93 (1H, d, J = 8.4Hz), 8.03 (1H, d, J = 1.4Hz).

Step 4

3-Methyl-5-(tetrazol-5-yl)-benzo[b]thiophene

To a solution of 5-cyano-3-methyl benzo[b]thiophene (0.194g, 1.12mmol) in N-methylpyrrolidinone (5ml) under nitrogen was added triethylamine hydrochloride (0.231g, 1.68mmol) followed by sodium azide (0.234g, 3.59mmol) and the mixture was extracted with ether (4 x 50ml). The combined ether extracts were dried ($MgSO_4$) and evaporated *in vacuo* to

and the mixture was stirred at 100°C for 2h. After cooling, the mixture was poured into water (10ml) and a brown solid was filtered off, washed with water and dried in a vacuum pistol to leave 73.5mg. The filtrate was extracted with dichloromethane (3 x 30ml) and the combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to leave 44.7mg. This was combined with the original solid and chromatographed on flash silica, eluting with 20-50% ethyl acetate/petroleum ether to yield 61.5mg (38%) of the title product as a white solid. δ ($CDCl_3$) 3.99 (2H, s), 4.43 (3H, s), 7.59 (1H, s), 8.00 (1H, d, J = 8.5Hz), 8.19 (1H, dd, J = 8.5 and 1.5Hz), 8.47 (1H, s).

Step 7

3-(2-Aminoethyl)-5-(2-methyl-tetrazol-5-yl) benzo[b]thiophene. Oxalate.

To a solution of 3-cyanomethyl-5-(2-methyl-tetrazol-5-yl) benzo[b]thiophene (0.434g, 1.70mmol) in THF (16ml) under nitrogen was added dropwise 1.0M borane-tetrahydrofuran complex in THF (5.10ml, 5.10mmol) and the mixture was heated at reflux for 6h. After cooling in an ice-bath the mixture was quenched with 2N HCl (22ml) and heated to reflux for 1h. The THF was then removed *in vacuo* and the residue basified with 50% sodium hydroxide solution (4ml) before extracting with dichloromethane (3 x 75ml). The combined extracts were dried (K_2CO_3) and evaporated *in vacuo* to leave 0.45g.

J = 8.4 and 1.5Hz), 8.51 (1H, s). *m/z* (CI^+,NH_3) 231 $(M+H)^+$ <u>1-isomer</u> δ ($CDCl_3$) 2.50 (3H, s), 4.22 (3H, s), 4.22 (3H, s), 7.23 (1H, s), 7.64 (1H, dd, J = 8.3 and 1.5Hz), 8.03 (1H, d, J = 8.4Hz), 8.12 (1H, d, J = 1.6Hz). *m/z* (CI^+,NH_3) 231 $(M+H)^+$, 202, 172.

<u>Step 6</u>

<u>3-Cyanomethyl-5-(2-methyltetrazol-5-yl) benzo[b]thiophene</u>

To a refluxing mixture of 3-methyl-5-(2-methyltetrazol-5-yl) benzo[b]thiophene (0.162g, 0.703mmol) and benzoyl peroxide (10.6mg) in carbon tetrachloride (10ml) irradiated with two desk lamps (2 x 60W) was added N-bromosuccinimide (0.126g, 0.707mmol) in small portions. After the addition was complete the mixture was heated at reflux for a further 90 min, then filtered and the filtrate was evaporated *in vacuo* to leave an oil/solid mixture. Chromatography on flash silica, eluting with dichloromethane gave 0.161g of crude 3-bromomethyl-5-(2-methyltetrazol-5-yl) benzo[b]thiophene as a colourless oil.

The crude 3-bromomethyl-5-(2-methyl-tetrazol-5-yl) benzo[b]thiophene (0.145g) in DMSO (0.3ml) was added to a mixture of sodium cyanide (29.9mg, 0.61mmol) in DMSO (0.2ml)

methyltetrazol-5-yl) benzo[b]thiophene.

The crude 3-bromo-5-(1-methyltetrazol-5-yl) benzo[b]thiophene (0.504g) was reacted with 97.7mg (1.99mmol) of sodium cyanide in 1.5ml of DMSO at 100°C for 2h. After cooling, the reaction mixture was poured into water (25ml) and extracted with dichloromethane (6 x 50ml). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to leave 0.37g. Chromatography on flash silica, eluting with 30-60% ethyl acetate/petroleum ether yielded 28.0mg (4%) of the title product. δ ($CDCl_3$) 4.00 (2H, s), 4.23 (3H, s), 7.63 (1H, s), 7.73 (1H, dd), 8.08 (1H, d), 8.15 (1H, d).

Step 2

3-(2-Aminoethyl)-5-(1-methyltetrazol-5-yl) benzo[b]thiophene. Oxalate.

Following the procedure of Example 11, Step 7, 26.1mg (0.102mmol) of 3-cyanomethyl-5-(1-methyltetrazol-5-yl) benzo[b]thiophene in 2ml of THF was reacted with 0.36ml (0.36mmol) of 1.0M borane-tetrahydrofuran complex in THF. Chromatography on flash silica, eluting with CH_2Cl_2/MeOH/NH_3(aq) (60:8:1) gave 17.7mg (67%) of the title product as a colourless oil. The oxalate salt was prepared using oxalic acid in methanol/ether to give the title product oxalate as a white solid, m.p. 206-212°C. Analysis found: C, 47.55; H, 4.05;

Chromatography on flash silica eluting with CH_2Cl_2/MeOH/NH_3(aq) (60:8:1) gave 0.383g (87%) of the title product as a white solid. The oxalate salt was prepared using oxalic acid in methanol/ether to give the title product oxalate as a white solid, m.p. 204-209°C. Analysis found: C, 47.75; H, 4.28; N, 19.28%. Calcd for $C_{12}H_{13}N_5S$. 1.1 $C_2H_2O_4$: C, 47.59; H, 4.28; N, 19.54%. δ (DMSO) 3.17-3.21 (4H, m), 4.46 (3H, s), 7.72 (1H, s), 8.06 (1H, dd, J = 8.4 and 1.4Hz), 8.52(1H, s) *m/z* (CI^+,NH_3) 260 $(M+H)^+$, 230.

EXAMPLE 12

3-(2-Aminoethyl)-5-(1-methyltetrazol-5-yl) benzo[b]thiophene. Oxalate.

Step 1

3-Cyanomethyl-5-(1-methyltetrazol-5-yl) benzo[b]thiophene

Following the procedure of Example 11, Step 6, 0.666g (2.89mmol) 3-methyl-5-(1-methyltetrazol-5-yl) benzo[b]thiophene was reacted with 0.515g (2.89mmol) of N-bromosuccinimide and 38.1mg of benzoyl peroxide in 30ml of carbon-tetrachloride. The reaction mixture was evaporated *in vacuo* and chromatographed on flash silica, eluting with 0-3% methanol/dichloromethane to give 0.532g of crude 3-bromo-5-(1-

8.4Hz), 8.56 (1H, s). m/z (CI^+,NH_3) 288 $(M+H)^+$.

EXAMPLE 14

N,N-Dimethyl-2-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine Trisoxalate

1. 1-(4-Nitrophenyl)methyl-2-methylimidazole

Sodium hydride (2.45g; 61.0mmol, 60% dispersion in oil) was added to a solution of 2-methylimidazole (5.0g, 60.9mmol) in DMF (100ml). The mixture was stirred at room temperature for 0.25h before adding 4-nitrobenzyl bromide (13.2g, 61.0mmol) and heating at 110°C for 2h followed by stirring at room temperature for 16h. Water (200ml) and ethyl acetate (500ml) were added, the aqueous separated and extracted with ethyl acetate (2 x 500ml). The combined extracts were washed with water (3 x 250ml), dried (MgSO4) and evaporated. The crude product was chromatographed on silica gel eluting with CH_2Cl_2/MeOH (4%) to give the title-product (1.58g, 10.5%); δ (360MHz, $CDCl_3$) 2.34 (3H, s, Me); 5.16 (2H, s, CH_2); 6.67 (1H, d, J = 1.3Hz, Ar-H); 7.03 (1H, d, J = 1.3Hz, Ar-H); 7.19 (2H, d, J = 9.5Hz, Ar-H); 8.22 (2H, d, J = 9.5Hz, Ar-H).

N, 19.65%. Calcd for $C_{12}H_{13}N_5S$. 1.1 $C_2H_2O_4$: C, 47.59; H, 4.28; N, 19.54%. δ (D_2O) 3.32-3.35 (2H,m), 3.40-3.44 (2H, m), 4.22 (3H, s), 7.64 (1H, s), 7.73 (1H, d, J = 8.4Hz), 8.19 (1H, s), 8.22 (1H, d, 8.5Hz).

EXAMPLE 13

3-[2-(N,N-Dimethylamino)ethyl]-5-(2-methyltetrazol-5-yl) benzo[b]thiophene. Oxalate.

To a mixture of -(2-aminoethyl)-5-(2-methyltetrazol-5-yl) benzo[b]thiophene (0.372g, 1.43mmol) and sodium cyanoborohydride (0.136g, 2.15mmol) in methanol (3ml) and acetic acid (0.247ml, 4.30mmol) cooled in an ice bath was added 38% w/v formaldehyde solution (0.453ml, 5.74mmol) in methanol (3ml) dropwise over 5min and the mixture was stirred at room temperature for 3h. After this time, saturated potassium carbonate solution (30ml) was added and the mixture was extracted with ethyl acetate (3 x 50ml). The combined extracts were evaporated *in vacuo* to leave 0.53g. Chromatography on flash silica, eluting with 10-30% methanol/dichloromethane, gave 0.335g (81%) of the title product as a colourless oil. The oxalate salt was prepared using oxalic acid in methanol/ether to give the title product oxalate as a white solid, m.p. 214-218°C. Analysis found: C, 50.58; H, 4.80; N, 18.28%. Calcd for $C_{14}H_{17}N_5S$. $C_2H_2O_4$: C, 50.92; H, 5.07; N, 18.56%. δ (DMSO) 2.84 (6H, s), 3.30-3.42 (4H, m), 4.46 (3H, s), 7.69 (1H, s), 8.06 (1H, dd, J = 8.4 and 1.4Hz), 8.20 (1H, d, J =

EXAMPLE 16

N,N-Dimethyl-2-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]ethylamine Sesquioxalate

1. 1-(4-Nitrophenyl)-2-methylimidazole

Sodium hydride (4.87g, 122.0mmol, 60% dispersion in oil) was added to a solution of 2-methylimidazole (10g, 122.0mmol) in DMF (100ml) and stirred at room temperature for 0.25h. 1-Fluoro-4-nitrobenzene (17.18g, 122.0mmol) was added to the reaction mixture and stirred at room temperature for 16h. Water (150ml) and ethyl acetate (250ml) were added, the aqueous separated and extracted with ethyl acetate (3 x 150ml). The combined extracts were washed with water (3 x 150ml), dried (Na_2SO_4) and evaporated to give the desired product (11.5g, 47%); δ (360MHz, $CDCl_3$) 2.24 (3H, s, Me); 7.06 (1H, d, J = 1.5Hz, Ar-H); 7.10 (1H, d, J = 1.5Hz, Ar-H); 7.50 (2H, d, J = 9.5Hz, Ar-H); 8.38 (2H, d, J = 9.5Hz, Ar-H).

2. N,N-Dimethyl-2-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]ethylamine Sesquioxalate

Prepared from the preceding 4-nitrophenyl imidazole using the procedure described for Example 5. The sesquioxalate salt was prepared, mp 185-186°C (iPA/MeOH); (Found: C, 56.17; H, 5.99; N, 13.46. $C_{16}H_{20}N_4.1.55\ (C_2H_2O_4).\ 0.1\ EtOH$ requires C,

2. N,N-Dimethyl-2-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl)ethylamine Trisoxalate

Prepared from the preceding 4-nitrobenzyl imidazole using the general procedure described for Example 5. The trisoxalate salt was prepared, mp 160-163°C ($MeOH/Et_2O$); (Found: C, 50.57; H, 5.25; N, 10.60. $C_{17}H_{22}N_4.2.8\ (C_2H_2O_4)$ requires C, 50.79; H, 5.21; N, 10.48%); m/e 282 (M^+); δ (360MHz, D_2O) 2.65 (3H, s, Me); 2.92 (6H, s, NMe_2); 3.25 (2H, t, J = 7.3Hz, CH_2); 3.50 (2H, t, J = 7.3Hz, CH_2); 5.42 (2H, s, CH_2); 7.18 (1H, d, J = 8.4Hz, Ar-H); 7.31-7.40 (2H, m, Ar-H); 7.40 (1H, s, Ar-H); 7.56 (1H, d, J = 8.4Hz, Ar-H); 7.66 (1H, s, Ar-H).

EXAMPLE 15

N,N-Dimethyl-2-[5-imidazol-1-ylmethyl-1H-indol-3-yl]ethylamine Bisoxalate

Prepared from imidazole and 4-nitrobenzyl bromide using the procedure described for Example 5. The bisoxalate salt was prepared, 165-166°C ($MeOH/Et_2O$); (Found: C, 53.30; H, 5.34; N, 12.18. $C_{16}H_{20}N_4$. 2.05 ($C_2H_2O_4$) requires C, 53.30; H, 5.36; N, 12.37%); δ (360MHz, D_2O) 2.92 (6H, s, NMe_2); 3.24 (2H, t, J = 7.7Hz, CH_2); 3.48 (2H, t, J = 7.7Hz, CH_2); 5.50 (2H, s, CH_2); 7.27 (1H, dd, J = 1.5 and 8.4Hz, Ar-H); 7.37 (1H, s, Ar-H); 7.45 (1H, s, Ar-H); 7.49 (1H, s, Ar-H); 7.56 (1H, d, J = 8.4Hz, Ar-H); 7.75 (1H, s, Ar-H); 8.78 (1H, s, Ar-H).

118-120°C; (Found: C, 58.76; H, 6.27; N, 17.79. $C_{15}H_{19}N_3.C_4H_6O_4$ requires C, 58.90; H, 6.50; N, 18.08%).

EXAMPLE 18

N,N-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Benzoate

The benzoate salt of N,N-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine was prepared by addition of a solution of benzoic acid in diethyl ether to a solution of the free base in ethanol/diethyl ether (1:4). The precipitated salt was recrystallised from ethanol, mp 178-180°C; (Found: C, 67.28; H, 6.55; N, 17.66. $C_{15}H_{19}N_3.C_6H_5CO_2H$ requires C, 67.50; H, 6.44; N, 17.89%); ^1H NMR (360MHz, D_2O) δ 2.92 (6H, s, NMe_2); 3.22 (2H, t, J = 7.3Hz, CH_2); 3.46 (2H, t, J = 7.3Hz, CH_2); 5.52 (2H, s, CH_2); 7.22 (1H, dd, J = 1.6 and 8.4Hz, Ar-H); 7.36 (1H, s, Ar-H); 7.44-7.58 (4H, m, Ar-H); 7.65 (1H, s, Ar-H); 7.87-7.91 (2H, m, Ar-H); 8.06 (1H, s, Ar-H); 8.54 (1H, s, Ar-H).

EXAMPLE 19

N,N-Dimethyl-2-[5-(2-ethyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

Prepared as described for Example 3, using ethyl iodide. The oxalate salt was prepared, mp 140-142°C; (Found: C, 55.71;

56.19; H, 5.79; N, 13.58%); δ (360MHz, D_2O) 2.55 (3H, s, Me); 2.93 (6H, s, NMe_2); 3.26 (2H, t, J = 7.4Hz, CH_2); 3.51 (2H, t, J = 7.4Hz, CH_2); 7.30 (1H, dd, J = 2.0 and 8.7Hz, Ar-H); 7.48 (1H, d, J = 2.1Hz, Ar-H); 7.51-7.53 (2H, m, Ar-H); 7.70 (1H, d, J = 8.7Hz, Ar-H); 7.79 (1H, d, J = 2.0Hz, Ar-H).

EXAMPLE 17

N,N-Dimethyl-2-[5-(1,2,4-triazol-1ylmethyl)-1H-indol-3-yl]ethylamine. Succinate. Procedure B

A solution of 1-(4-hydrazinophenyl)methyl-1,2,4-triazole dihydrochloride (2g, 7.6mmol, Example 5 step 3) and 4-N,N-dimethylaminobutanal dimethylacetal (1.8g, 11.2mmol) in 4% aqueous sulphuric acid (70ml) was heated at reflux for 2h. After the reaction mixture was cooled to room temperature, ethyl acetate (200ml) was added and the aqueous basified with K_2CO_3. The aqueous was separated and extracted further with ethyl acetate (2 x 150ml). The combined organics were dried (Na_2SO_4) and evaporated, and the residue chromatographed on silica gel eluting with CH_2Cl_2/EtOH/NH_3 (30:8:1) to give the title-triazole (610mg, 30%). The succinate salt was prepared by addition of a solution of succinic acid (0.27g, 2.3mmol) in methanol (3ml) to a solution of the triazole (0.61g, 2.3mmol) in methanol (5ml). The solvent was removed under vacuum and the resultant product recrystallised from isopropylalcohol, mp

Prepared as described for Example 16 from 1,2,4-triazole sodium derivative and 1-fluoro-4-nitrobenzene. The bisoxalate salt was prepared, mp 210°C ($MeOH/Et_2O$); (Found: C, 50.11; H, 4.78; N, 16.35. $C_{14}H_{17}N_5$. 1.9 ($C_2H_2O_4$) requires C, 50.14; H, 4.92; N, 16.43%); ^{1}H NMR (360MHz, D_2O) δ 2.92 (6H, s, NMe_2); 3.25 (2H, t, J = 7.4Hz, CH_2); 3.50 (2H, t, J = 7.4Hz, CH_2); 7.44 (1H, s, Ar-H); 7.47 (1H, dd, J = 2.0 and 8.7Hz, Ar-H); 7.63 (1H, d, J = 8.7Hz, Ar-H); 7.88 (1H, d, J = 2.0Hz, Ar-H); 8.36 (1H, s, Ar-H); 9.05 (1H, s, Ar-H).

EXAMPLE 22

4-[5-(2-Methylimidazol-1-yl)-1H-indol-3-yl]-N-methylpiperidine. Bisoxalate sesquihydrate

A solution of N-methyl-4-(formylmethyl)piperidine (0.25g, 1.8mmol) and 4-(2-methylimidazolyl)phenyl hydrazine hydrochloride (0.48g, 2.1mmol) in 4% H_2SO_4 (25ml) was heated at reflux for 16h. The mixture was cooled to room temperature, basified with K_2CO_3 solution and extracted with CH_2Cl_2 (3 x 75ml). The combined extracts were dried (Na_2SO_4) and evaporated and the residue purified by chromatography on silica-gel eluting with $CH_2Cl_2/EtOH/NH_3$ (60:8:1) to give the title-compound (0.12g). The bisoxalate sesquihydrate salt was prepared, mp 65-70°C (hygroscopic); (Found: C, 52.97; H, 5.51; N, 11.07. $C_{18}H_{22}N_4.2(C_2H_2O_4).1.5H_2O$ requires C, 52.69; H, 5.83; N, 11.17%); ^{1}H NMR (360MHz, D_2O) δ 1.96-2.08 (2H, m, CH_2); 2.31-2.40 (2H, m, CH_2); 2.56 (3H, s, CH_3); 2.95 (3H, s,

H, 6.26; N, 21.35. $C_{16}H_{22}N_6.C_2H_2O_4$ requires C, 55.66; H, 6.23; N, 21.64%); ^{1}H NMR (360MHz, D_2O) δ 1.54 (3H, t, J = 7.4Hz, CH_3); 2.91 (6H, s, NMe_2); 3.21 (2H, t, J = 7.4Hz, CH_2); 3.47 (2H, t, J = 7.4Hz, CH_2); 4.34 (2H, s, CH_2); 4.64 (2H, q, J = 7.4Hz, $\underline{CH_2}CH_3$); 7.17 (1H, dd, J = 1.5 and 8.4Hz, Ar-H); 7.33 (1H, s, Ar-H); 7.48 (1H, d, J = 8.4Hz, Ar-H); 7.59 (1H, s, Ar-H).

EXAMPLE 20

N,N-Dimethyl-2-[5-(1-ethyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

Prepared using the procedure described for Example 4, using ethyl iodide. The oxalate salt was prepared, mp 179°C ($MeOH/Et_2O$); (Found: C, 55.59; H, 6.23; N, 21.49. $C_{16}H_{22}N_6.C_2H_2O_4$ requires C, 55.66; H, 6.23; N, 21.64%); ^{1}H NMR (360MHz, D_2O) δ 1.32 (3H, t, J = 7.4Hz, CH_3); 2.90 (6H, s, NMe_2); 3.21 (2H, t, J = 7.4Hz, CH_2); 3.46 (2H, t, J = 7.4Hz, CH_2); 4.38 (2H, q, J = 7.4Hz, CH_2); 4.47 (2H, s, CH_2); 7.14 (1H, dd, J = 1.5 and 8.4Hz, Ar-H); 7.35 (1H, s, Ar-H); 7.50 (1H, d, J = 8.4Hz, Ar-H); 7.53 (1H, s, Ar-H).

EXAMPLE 21

N,N-Dimethyl-2-[5-(1,2,4-triazol-1-yl)-1H-indol-3-yl]ethylamine. Bisoxalate

EXAMPLE 24

1H-4-[5-(2-Methylimidazol-1-yl)-1H-indol-3-yl]-piperidine. Bisoxalate dihydrate

1. 4-[5-(2-Methylimidazol-1-yl)-1H-indol-3-yl]-N-benzylpiperidine

Prepared from N-benzyl-4-(formylmethyl)piperidine using the procedure described for Example 22; ^{1}H NMR (360MHz, $CDCl_3$) δ 1.80-1.94 (2H, m, CH_2); 1.98-2.06 (2H, m, CH_2); 2.14-2.24 (2H, m, CH_2); 2.33 (3H, s, CH_3); 2.76-2.85 (1H, m, CH); 3.02-3.08 (2H, m, CH_2); 3.60 (2H, s, CH_2); 7.03-7.10 (4H, m, Ar-H); 7.26-7.38 (5H, m, Ar-H); 7.41 (1H, d, J = 8.5Hz, Ar-H); 7.52 (1H, d, J = 1.8Hz, Ar-H); 8.30 (1H, br s, NH).

2. 1H-4-[5-(2-Methylimidazol-1-yl)-1H-indol-3-yl]-piperidine. Bisoxalate dihydrate

To a solution of ammonium formate (0.32g, 5.07mmol) and 4-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]-N-benzylpiperidine (0.4g, 1.08mmol), in methanol (40ml) was added Pd/C (10%; 0.4g) and the mixture stirred at 60°C for 3h. The catalyst was removed by filtration through celite and the solvent removed under vacuum. The residue was taken up into H_2O (30ml), basified with NH_3 solution and extracted with ethyl acetate (3 x 100ml). The combined extracts were dried (Na_2SO_4) and

CH_3); 3.20-3.27 (3H, m, CH and CH_2); 3.64-3.68 (2H, m, CH_2); 7.28 (1H, dd, J = 2 and 8.7Hz, Ar-H); 7.44 (1H, s, Ar-H); 7.48 (1H, d, J = 2Hz, Ar-H); 7.53 (1H, d, J = 2Hz, Ar-H); 7.69 (1H, d, J = 8.7Hz, Ar-H); 7.81 (1H, d, J = 2Hz, Ar-H).

EXAMPLE 23

4-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]-N-methylpiperidine. Oxalate

A solution of N-methyl-4-(formylmethyl)piperidine (0.1g, 0.71mmol) and 4-(1,2,4-triazolylmethyl)phenyl hydrazine dihydrochloride (0.185g, 0.71mmol) in 4% H_2SO_4 was heated at reflux for 2h. The mixture was cooled to room temperature, basified with K_2CO_3 solution and extracted with CH_2Cl_2 (2 x 100ml). The crude product was chromatographed on silica-gel eluting with CH_2Cl_2/EtOH/NH_3 (40:8:1) to give the title-compound (60mg). The oxalate salt was prepared, mp 218-220°C; (Found: C, 58.61; H, 6.03; N, 17.94. $C_{17}H_{21}N_5$.1.02 ($C_2H_2O_4$) requires C, 58.96; H, 6.38; N, 17.56%); ^{1}H NMR (360MHz, D_2O) δ 1.88-2.02 (2H, m, CH_2); 2.20-2.34 (2H, m, CH_2); 2.92 (3H, s, CH_3); 3.10-3.24 (3H, m, CH and CH_2); 3.60-3.64 (2H, m, CH_2); 5.51 (2H, s, CH_2); 7.21 (1H, dd, J = 1.5 and 8.4Hz, Ar-H); 7.26 (1H, s, Ar-H); 7.51 (1H, d, J = 8.4Hz, Ar-H); 7.69 (1H, s, Ar-H); 8.05 (1H, s, Ar-H); 8.55 (1H, s, Ar-H).

EXAMPLE 26

1H-4-[5-(2-Methylimidazol-1-yl)-1H-indol-3-yl]-pyrrolidine. Bisoxalate

1. 3-[5-(2-Methylimidazol-1-yl)-1H-indol-3-yl]-N-benzylpyrrolidine

Prepared from N-benzyl-3- (formylmethyl)pyrrolidine and 4-(2-methylimidazolyl)phenyl hydrazine hydrochloride as described for Example 22; ^{1}H NMR (360MHz, $CDC1_3$) δ 1.98-2.06 (1H, m, CH of CH_2); 2.34 (3H, s, CH_3); 2.34-2.44 (2H, m, 2 of CH of CH_2); 2.71 (1H, t, J = 7.4 Hz, CH of CH_2); 2.80 (1H, t, J = 6.9Hz, CH of CH_2); 3.05 (1H, t, J = 8.7Hz, CH of CH_2) 3.61-3.73 (1H, m, CH); 3.72 (2H, ABq, J = 13Hz, CH_2); 6.95-7.14 (4H, m, Ar-H); 7.22-7.41 (5H, m, Ar-H); 7.40 (1H, d, J = 8.5Hz, Ar-H); 7.66 (1H, s, Ar-H); 8.30 (1H, br s NH).

2. 1H-4-[5-(2-Methylimidazol-1-yl)-1H-indol-3-yl]-pyrrolidine. Bisoxalate

Prepared from the preceding N-benzylpyrrolidine using the procedure described for Example 24. The bisoxalate salt was prepared, mp 210-213^{o}C (methanol/ether); (Found: C, 53.93; H, 5.22; N, 12.50. $C_{16}H_{18}N_4.2(C_2H_2O_4)$ requires C, 53.81; H, 4.97; N, 12.55%); ^{1}H NMR (360MHz, D_2O) δ 2.91-2.30 (1H, m, CH of CH_2); 2.55 (3H, s, CH_3); 2.55-2.60 (1H, m, CH of CH_2); 3.35-3.64 (3H, m, CH and CH_2); 3.80-3.90 (2H, m, CH_2); 7.30

evaporated and the residue chromatographed through silica-gel eluting with $CH_2Cl_2/MeOH/NH_3$ (30:8:1) to give the desired piperidine (0.2g). The bisoxalate dihydrate salt was prepared, mp 80°C (hygroscopic); (Found: C, 50.53; H, 5.54; N, 10.87. $C_{17}H_{20}N_4.2(C_2H_2O_4).2.2H_2O$ requires C, 50.43; H, 5.72; N, 11.20%); ^{1}H NMR (360MHz, D_2O) δ 1.91-2.03 (2H, m, CH_2); 2.30-2.34 (2H, m, CH_2); 2.55 (3H, s, CH_3); 3.19-3.36 (3H, m, CH and CH_2); 3.55-3.62 (2H, m, CH_2); 7.28 (1H, dd, J = 1.2 and 8.6Hz, Ar-H); 7.44 (1H, s, Ar-H); 7.47 (1H, d, J = 2.0Hz, Ar-H); 7.52 (1H, d, J = 2.0Hz, Ar-H); 7.69 (1H, d, J = 8.6Hz, Ar-H); 7.82 (1H, d, J = 1.2Hz, Ar-H).

EXAMPLE 25

1H-4-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]-piperidine. Oxalate

Prepared from N-benzyl-4-(formylmethyl)piperidine and 4-(1,2,4-triazolylmethyl)phenyl hydrazine dihydrochloride using the procedures described for Examples 23 and 24. The oxalate salt was prepared, mp 272°C; (Found: C, 58.27; H, 5.56; N, 18.79. $C_{16}H_{19}N_5.C_2H_2O_4$ requires C, 58.21; H, 5.70; N, 18.86%); ^{1}H NMR (360MHz, D_2O) δ 1.86-1.98 (2H, m, CH_2); 2.24-2.28 (2H, m, CH_2); 3.15-3.36 (3H, m, CH and CH_2); 3.52-3.56 (2H, m, CH_2); 5.51 (2H, s, CH_2); 7.21 (1H, dd, J = 1.6 and 8.5Hz, Ar-H); 7.27 (1H, s, Ar-H); 7.52 (1H, d, J = 8.5Hz, Ar-H); 7.70 (1H, d, J = 1.6Hz, Ar-H); 8.09 (1H, s, Ar-H); 8.60 (1H, s, Ar-H).

(1H, dd, J = 2 and 8.6Hz, Ar-H); 7.47 (1H, d, J - 2Hz, Ar-H); 7.50 (1H, s, Ar-H); (7.53 (1H, d, J = 2Hz, Ar-H); 7.70 (1H, d, J = 8.6Hz, Ar-H); 7.80 (1H, d, J = 2Hz, Ar-H).